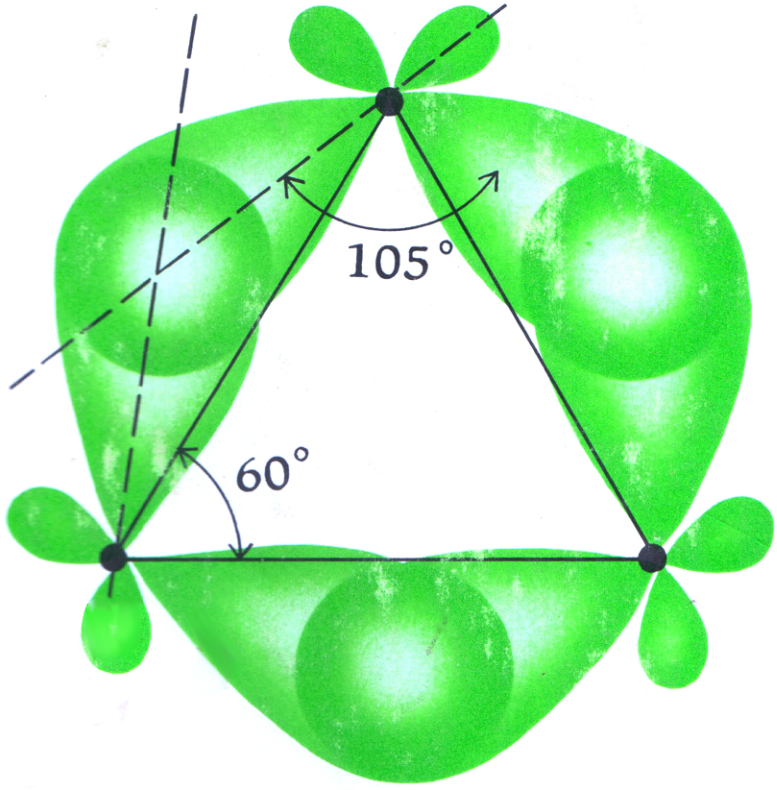
FUNDAMENTALS OF ORGANIC CHEMISTRY

A.N. NESMEYANOV, N.A. NESMEYANOV



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FUNDAMENTALS OF ORGANIC CHEMISTRY

by
A.N. Nesmeyanov
and
N.A. Nesmeyanov

This book is Volume I of the four-volume textbook intended for a systematic study of organic chemistry. The material is divided into two parts and covers a considerably wider field than the normal university treatment of the subject. Part One (the first three volumes) is constructed on "classical" lines. Part Two (volume IV) is intended for attentive reading rather than for close study.

Volume I comprises the following sections – introduction, aliphatic (saturated and unsaturated) compounds. The material is presented in order of increasing sophistication – first, rather simply and in detail, and then in more and more concise form.

This book has been translated from the second revised Russian edition published in two volumes in 1974. The first Russian edition (in two volumes) was published in 1969.

This book may be used for self-study and for reading the course of organic chemistry at universities and chemical higher schools. It will undoubtedly be of interest to post-graduates, teachers and young scientists and engineers working in the field of organic chemistry.

FUNDAMENTALS OF ORGANIC CHEMISTRY

Volume II

А. Н. Несмеянов, Н. А. Несмеянов

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ACYCLIC COMPOUNDS
(continued)

Chapter 4

Heterofunctional Compounds

Heterofunctional compounds are compounds containing two or more different functional groups. The number of such combinations is evidently legion. We shall consider only the most important compounds, beginning with aminoalcohols and combinations of the carboxyl group with other groups (OH, C=O, NO_2, NH_2) and passing then over to combinations of the carbonyl group with other groups (chiefly, with OH). It is exactly these types that many important natural compounds belong to.

In studying the various combinations of functional groups we shall direct our attention to new properties arising in such combinations without resorting to the already familiar behaviour of individual functional groups. The closer are the functional groups to each other, the more sharply pronounced is their interaction and the more prominent are the new properties of the combination. This may be illustrated by the example of a combination of a hydroxyl and a carbonyl group which are joined together into a carboxyl group—a completely new function which differs sharply from the hydroxyl and carbonyl groups taken separately.

4.1. Aminoalcohols

When formaldehyde is allowed to react with secondary amines, methylol derivatives of the amines can be isolated in certain cases, which are converted into methylene bis-amines provided that an excess of the amine is present:

$$CH_2O + HNR_2 \rightarrow HO-CH_2-NR_2 \xrightarrow{HNR_2} R_2N-CH_2-NR_2 + H_2O$$

The hydroxyl group of the methylol derivatives of amines is easily eliminated in the form of water with the sufficiently mobile

hydrogen atom of the second reagent. This happens, for example, in the Mannich reaction which proceeds by the following scheme:

$$R'H + CH_2O + HNR_2 \longrightarrow R'H + [HOCH_2NR_2] \longrightarrow R' - CH_2 - NR_2 + H_2O$$

where R'H is an aliphatic compound with an active hydrogen atom or an aromatic compound.

Methylol compounds do not, in principle, belong to aminoalcohols because they are functional derivatives of formaldehyde and their reactions are specifically different.

The simplest true aminoalcohol, **2-aminoethanol** or **ethanolamine** (*colamine*), can be obtained by the interaction of ammonia with ethylene oxide:

$$H_2C\text{—}CH_2 + NH_3 \longrightarrow HOCH_2 - CH_2 - NH_2$$
$$\quad\ \backslash O /$$

Depending on the ratio of the reagents, the same easily proceeding reaction may lead to **diethanolamine** or **triethanolamine**:

$$2H_2C\text{—}CH_2 + NH_3 \longrightarrow (HOCH_2CH_2)_2NH$$
$$\quad\ \backslash O /$$

$$3H_2C\text{—}CH_2 + NH_3 \longrightarrow (HOCH_2CH_2)_3N$$
$$\quad\ \backslash O /$$

Another route to the preparation of aminoalcohols with a primary amino group is based on the interaction of the nitro derivatives of aliphatic hydrocarbons with formaldehyde:

$$CH_2O + CH_3NO_2 \longrightarrow HOCH_2 - CH_2NO_2 \xrightarrow{H_2/Ni} HOCH_2 - CH_2NH_2$$

$$3CH_2O + CH_3NO_2 \longrightarrow (HOCH_2)_3CNO_2 \xrightarrow{H_2/Ni} (HOCH_2)_3CNH_2$$

The properties of some aminoalcohols are given in Table 4.1.

The most widely used aminoalcohol is triethanolamine [TEA; tri-(2-hydroxyethyl)amine] which serves as an absorbent of CO_2 and other acid gases in gas-purifying processes (for example, in the purification of hydrogen). The triethanolamine that absorbed carbon dioxide loses it on heating and is thus regenerated. It also finds application as a harmless softening agent and plasticizer in the textile industry, for soap pastes, etc.

When the hydroxyl groups are replaced by chlorine (through the action of HCl or PCl_3), triethanolamine changes to tris-(β-chloroethyl)-amine, $(ClCH_2CH_2)_3N$, which is the analogue of yperite, $(ClCH_2CH_2)_2S$, by structure and vesicant action.

The grouping $(ClCH_2CH_2)_2N-$ is contained in the molecule of sarcolysine and other cancerolytic drugs.

TABLE 4.1. **Aminoalcohols**

Formula	Name	m.p., °C	b.p., °C	Density, d_4^{20}	K_b (at 25 °C)
$HOCH_2-CH_2-NH_2$	Ethanolamine or colamine	10.5	172.2	1.0180	3.63×10^{-10}
$HOCH_2-CH_2-N(CH_3)_2$	2-Dimethylaminoethanol	—	135	0.8866	—
$[HOCH_2-CH_2-\overset{+}{N}(CH_3)_3]OH^-$	Choline or trimethyl-β-hydroxyethylammonium hydroxide	Viscous liquid	—	—	8.77×10^{-6}
$(HOCH_2-CH_2)_2NH$	Diethanolamine or di-(2-hydroxyethyl)-amine	28	268	1.0966	1.32×10^{-9}
$(HOCH_2-CH_2)_3N$	Triethanolamine or tri-(2-hydroxyethyl)amine	21.2	279 (at 50 mm Hg)	1.1242	1.70×10^{-8}

The methylation of ethanolamine via the stages of monomethylaminoethanol and dimethylaminoethanol yields a trimethylethanolammonium salt:

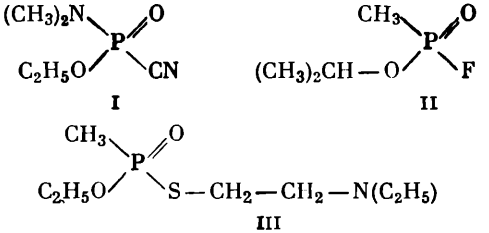
$$HOCH_2-CH_2-NH_2+3CH_3I \longrightarrow HOCH_2-CH_2-\overset{+}{\underset{CH_3}{\overset{CH_3}{N}}}-CH_3\ ^-I$$

The action of moist silver oxide on this salt is used to synthesize **choline** (trimethylethanolammonium hydroxide):

$$HOCH_2-CH_2-\overset{+}{\underset{CH_3}{\overset{CH_3}{N}}}-CH_3\ ^-OH$$

Choline plays an important part in the regulation of metabolism in the animal organism and is comparable to vitamins in its effect. Its acetate ester, choline acetate, which is commonly known as **acetylcholine** and serves as a mediator (a chemical transmitter) in the functioning of the nervous system, is liberated at nerve endings

in the transmission of nerve-to-muscle impulses. Acetylcholine exerts an exceptionally strong physiological effect. When administered into the body acetylcholine causes the contraction of the muscles, convulsions, the intensive peristalsis of the intestines, and, in contrast to choline itself, causes a rapid fall in blood pressure. Acetylcholine released at nerve endings and having played its part in the transmission of nervous impulses is instantly hydrolysed by the action of the enzyme acetylcholinesterase (or cholinesterase) to choline which has a relatively weak (and opposite in many respects) physiological effect. The inactivation of cholinesterase is tantamount in its effect to the administration of acetylcholine itself. Such deactivation is accomplished by so-called **nerve gases,** such as Tabun I, Sarin II and the even more toxic substance (III) discovered by the Swedish scientist Tammelin:

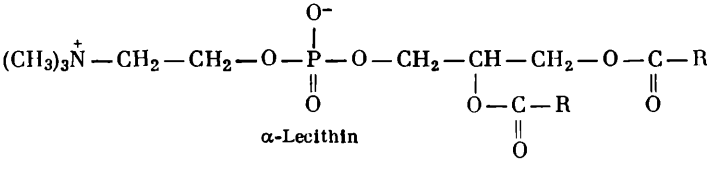


I II III

or by insecticides (in insects) like Thiophos, mercaptophos, M-81, and others (see Volume IV, "Organoelement Compounds").

The dehydration of choline leads to the formation of **neurine,** $CH_2=CH-\overset{+}{N}(CH_3)_3OH^-$ (trimethylvinylammonium hydroxide; a toxic substance).

Choline occurs in a combined form (choline phosphate) in a variety of substances belonging to a class of lipids, known as **phosphatides** or **phospholipids.** Typical phospholipids are the compounds known as **lecithins** (see Volume I, page 416). Lecithins are built just as the mixed glycerides of fatty acids and choline phosphate, i.e., one of their possible formulas is a formula of the following type:



α-Lecithin

There are also **cephalins** (*kephalins*) which have a structure of the same type based on monoethanolamine. Lecithins are in most cases found associated with fats and are a constituent of food in which they serve as one of the sources of phosphoric acid necessary to life.

4.2. Hydroxy Acids

Hydroxy acids are carboxylic acids that have a second function—a hydroxyl group.

The hydroxy acids are derived from the fatty acids by replacing a hydrogen atom of the hydrocarbon radical by a hydroxyl group.

The first and specific member of a series of hydroxy acids is hydroxyformic acid, i.e., carbonic acid

$$\begin{array}{c} HO-C-OH \\ \| \\ O \end{array}$$

A. Carbonic Acid and Its Derivatives

In distinction to other hydroxy acids in which the hydroxyl group, being more remote from the carboxyl group, has an alcoholic character, the hydroxyls of carbonic acid are united with the carbonyl group, no differences being observed between them: they are carboxyl-hydroxyl groups. Therefore, carbonic acid, which formally belongs to the class of hydroxy acids, is in fact closer to (though also considerably different from) the dicarboxylic acids. In essence, carbonic acid is an exceptional compound because of its properties and also because it has no homologues since any substitution reaction in it leads to the formation of a functional derivative. For this reason we shall consider carbonic acid separately from other hydroxy acids.

Carbonic acid exists only in weak aqueous solutions (solutions of carbon dioxide in water), the equilibrium in such solutions

$$CO_2 + H_2O \rightleftarrows H_2CO_3$$

being strongly displaced to the left, which is what gives an impression of the weakly acidic character of carbonic acid. The measured concentration of hydrogen ions is referred to the entire concentration of carbon dioxide, whereas in actual fact only a small portion of CO_2 is hydrated in H_2CO_3.

(a) *Functional Derivatives of Carbonic Acid*

The formulas, names and physical properties of a number of derivatives of carbonic acid are presented in Table 4.2.

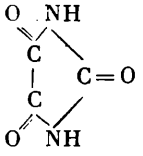
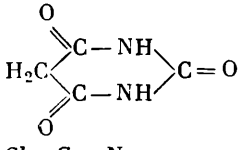
The salts of carbonic acid are not discussed in this book since they are studied in a course of general chemistry.

The acid chloride of carbonic acid, **carbonyl chloride** or **phosgene**, $COCl_2$, is produced by direct combination of carbon monoxide and chlorine (either by exposing the mixture to the direct rays of the sun or in the presence of activated charcoal) and is an important

TABLE 4.2. **Derivatives of Carbonic Acid**

Formula	Name	m.p., °C	b.p., °C	Density, d_4^{20}
$HO-C(=O)-OH$	Carbonic acid	−58.6 (at 5.2 kg/cm²)	−78.5 (subl.)	1.56 (at −79°C, solid) 1.101 (at −37°C, liquid)
$Cl-C(=O)-Cl$	Phosgene or carbonyl chloride	−118	+8.3	1.392 (d_4^{19})
$Cl-C(=O)-OCH_3$	Methyl chlorocarbonate or methyl chloroformate	—	71.4	1.236 (at 15°C)
$Cl-C(=O)-OC_2H_5$	Ethyl chlorocarbonate or ethyl chloroformate	−80.6	94	1.138
$CH_3O-C(=O)-OCH_3$	Dimethyl carbonate	+0.5	91	1.0694
$C_2H_5O-C(=O)-OC_2H_5$	Diethyl carbonate	−43	126.8	0.9751
$C(OCH_3)_4$	Tetramethyl orthocarbonate	—	—	—
$C(OC_2H_5)_4$	Tetraethyl orthocarbonate	—	159	0.9186
$NH_2-C(=O)-OCH_3$	Methyl carbamate	+52	177	1.136 (d_4^{50})
$NH_2-C(=O)-OC_2H_5$	Ethyl carbamate or urethane	50	180	0.9862 (d_4^{21})
$NH_2-C(=O)-NH_2$	Carbamide or urea	132.7	Dec.	1.335
$Cl-C(=O)-NH_2$	Carbamoyl chloride	−50	61-62	—
$NH_2-C(=O)-NHCH_3$	Methylurea	+101	Dec.	1.204
$NH_2-C(=NH)-NH_2$	Guanidine	50	—	—

Table 4.2 (continued)

Formula	Name	m.p., °C	b.p., °C	Density, d_4^{20}
	Oxalylurea or parabanic acid	243 (dec.)	about 100 (subl.)	—
	Malonylurea or barbituric acid	245 (dec.)	—	—
$Cl-C\equiv N$	Cyanogen chloride	−6	13.8; 23.5	1.186
$HO-C\equiv N$	Cyanic acid	−79	Dec.	1.140 (d_4^0, liquid)
$C_2H_5O-C\equiv N$	Ethyl cyanate	—	162 (dec.)	0.890
$NH_2-C\equiv N$	Cyanamide	+44	140 (at 19 mm Hg)	1.0729 (d_4^{18})

industrial product. Phosgene has a very penetrating, choking smell. It is a highly toxic gas and was used extensively during World War I as a chemical warfare agent. Phosgene boils at 8.3°C, dissolves well in hydrocarbons, and is slowly hydrolysed by water:

$$COCl_2 + H_2O \longrightarrow CO_2 + 2HCl$$

It is rapidly hydrolysed by alkalis.

With alcohols, phosgene forms the esters of chlorocarbonic (chloroformic) acid which does not exist in the free state:

$$Cl-\underset{\underset{O}{\|}}{C}-Cl + CH_3OH \longrightarrow Cl-\underset{\underset{O}{\|}}{C}-OCH_3 + HCl$$

In a more vigorous reaction with excess alcohol the second chlorine atom also reacts, as a result of which the ester of carbonic acid is formed:

$$Cl-\underset{\underset{O}{\|}}{C}-OCH_3 + CH_3OH \longrightarrow CH_3O-\underset{\underset{O}{\|}}{C}-OCH_3 + HCl$$

Both these esters can be completely chlorinated; the former is called **diphosgene** and the latter, **triphosgene:**

$$Cl-\underset{\underset{O}{\|}}{C}-OCH_3+3Cl_2 \longrightarrow Cl-\underset{\underset{O}{\|}}{C}-OCCl_3+3HCl$$

$$CH_3O-\underset{\underset{O}{\|}}{C}-OCH_3+6Cl_2 \longrightarrow CCl_3O-\underset{\underset{O}{\|}}{C}-OCCl_3+6HCl$$

The smell and toxic properties of these esters resemble those of phosgene. On pyrolysis they are converted to phosgene:

$$Cl-\underset{\underset{O}{\|}}{C}-OCCl_3 \longrightarrow 2COCl_2 \qquad CCl_3O-\underset{\underset{O}{\|}}{C}-OCCl_3 \longrightarrow 3COCl_2$$

Such a conversion takes place in many reactions too. For instance, with alcohols, ammonia or amines these compounds react in just the same way as phosgene.

The esters of carbonic acid can also be made by the alkylation of the silver salt of carbonic acid with alkyl halides. They are hydrolysed in acid and alkaline solutions, like all esters of carbonic acid. No acid esters of carbonic acid exist, but their salts are known, which are prepared by the reaction of carbon dioxide with sodium alkoxides:

$$CO_2+RONa \longrightarrow R-O-\underset{\underset{O}{\|}}{C}-ONa$$

which when acidified decompose instantly:

$$R-O-\underset{\underset{O}{\|}}{C}-ONa+HCl \longrightarrow ROH+CO_2+NaCl$$

There are cyclic esters of carbonic acid, say, the ester formed by the interaction of phosgene with ethylene glycol:

$$\begin{array}{l} CH_2OH \\ | \\ CH_2OH \end{array} + \begin{array}{l} Cl \\ \diagdown \\ \quad C=O \\ \diagup \\ Cl \end{array} \longrightarrow \begin{array}{l} CH_2-O \\ | \quad \diagdown \\ | \qquad C=O \\ | \quad \diagup \\ CH_2-O \end{array} + 2HCl$$

Orthocarbonic esters (orthocarbonates) are obtained by the action of carbon tetrachloride, CCl_4 (or better chloropicrin, CCl_3NO_2) on sodium alkoxides:

$$CCl_3NO_2+4NaOR \longrightarrow C(OR)_4+3NaCl+NaNO_2$$

The hydrolysis (in acid medium) of orthocarbonic esters proceeds in two stages, just as in the case of all orthoesters. A neutral ester is first formed:

$$C(OR)_4+H_2O \xrightarrow{H^+} (RO)_2C=O+2ROH$$

which is then also hydrolysed.

With a Grignard reagent orthocarbonic esters give orthoesters of the corresponding acids:

$$RMgCl + C(OC_2H_5)_4 \longrightarrow RC(OC_2H_5)_3 + C_2H_5OMgCl$$

(b) *Sulphur Derivatives of Carbonic Acid*

Carbon disulphide (carbon bisulphide), CS_2, is the analogue of carbon dioxide. It is a liquid boiling at 46°C; its density is $d_4^{20} = 1.262$. The commercial product has a most disagreeable odour which resembles the odour of radish. Pure carbon disulphide has a pleasant ethereal odour somewhat similar to that of chloroform. Carbon disulphide is very inflammable, burning in air even when in contact with a heated glass rod. It is produced by the direct interaction of wood charcoal or coke and sulphur at a red heat. The major proportion of carbon disulphide is used in the manufacture of viscose silk from cellulose (see page 154). From carbon disulphide there is also obtained carbon tetrachloride:

$$CS_2 + 3Cl_2 \longrightarrow CCl_4 + S_2Cl_2$$

With Na_2S carbon disulphide forms sodium trithiocarbonate, Na_2CS_3, which is the analogue of sodium carbonate. The reaction with alkali gives the salt of **dithiocarbonic acid:**

$$CS_2 + 2NaOH \longrightarrow \begin{matrix} NaO \\ \diagdown \\ C=S \\ \diagup \\ NaS \end{matrix} + H_2O$$

With metal alkoxides carbon disulphide forms **salts of xanthic acids:**

$$CS_2 + NaOC_2H_5 \longrightarrow \begin{matrix} C_2H_5O \\ \diagdown \\ C=S \\ \diagup \\ NaS \end{matrix}$$

Free xanthic acids of the general formula

$$\begin{matrix} RO \\ \diagdown \\ C=S \\ \diagup \\ HS \end{matrix}$$

are themselves unstable and when formed on acidification of their salts decompose instantly with the formation of the original alcohol and carbon sulphide.

The salts of xanthic acid are alkylated to prepare the esters of dithiocarbonic acid:

$$\begin{matrix} C_2H_5O \\ \diagdown \\ C=S \\ \diagup \\ NaS \end{matrix} + CH_3I \longrightarrow \begin{matrix} C_2H_5O \\ \diagdown \\ C=S \\ \diagup \\ CH_3S \end{matrix} + NaI$$

When heated these esters decompose smoothly with the formation of an olefin and elimination of a mercaptan and carbon sulphoxide:

$$\begin{matrix} C_2H_5O \\ \diagdown \\ \quad C=S \\ \diagup \\ CH_3S \end{matrix} \longrightarrow CH_2=CH_2+COS+CH_3SH$$

The splitting-off of methyl mercaptan and carbon sulphoxide occurs at the *cis*-position, which can be established in the case of their elimination from alicyclic systems. Such a *cis*-elimination does not occur frequently.

This pathway to the preparation of an olefin is called the **Chugaev reaction** and is valuable in the investigation of alcohols of complicated structure, which give, as a result of this reaction, an olefin without isomerization. Isomerization often occurs when an acid or an acid catalyst of dehydration is used. The Chugaev reaction is apparently of no value for the preparation of the simplest olefins.

(c) *Nitrogen Derivatives of Carbonic Acid*

Urea, or *carbamide*, the diamide of carbonic acid, has long been known as a substance with the aid of which the human body is freed from excess nitrogen. Urea was discovered in urine by Hilaire-Marin Rouelle (1773). It occurs in human urine to the extent of about 2 per cent. At present large amounts of urea are produced from a mixture of carbon dioxide and ammonia at 200°C under pressure:

$$CO_2+2NH_3 \longrightarrow NH_2-\underset{\underset{O}{\|}}{C}-NH_2+H_2O$$

This is the most economical method of synthesizing urea. Formerly it was prepared by the hydrolysis of calcium cyanamide, which in its turn was made from calcium carbide by heating up to a high temperature in an atmosphere of nitrogen:

$$CaC_2+N_2 \longrightarrow CaN-C\equiv N+C$$

$$CaN-C\equiv N+2H_2O \longrightarrow H_2N-C\equiv N+Ca(OH)_2$$

$$H_2N-C\equiv N \xrightarrow{H_2O} H_2N-\underset{\underset{O}{\|}}{C}-NH_2$$

The constitution of urea is proved by its synthesis from phosgene acted on by ammonia:

$$Cl-\underset{\underset{O}{\|}}{C}-Cl+4NH_3 \longrightarrow NH_2-\underset{\underset{O}{\|}}{C}-NH_2+2NH_4Cl$$

Finally, let us recall that the first synthesis of urea was effected by Wöhler in 1828 by the isomerization (intramolecular rearrange-

ment) of ammonium cyanate which was heated in aqueous solution:

$$NH_4^+CNO^- \longrightarrow H_2N-\underset{\underset{O}{\|}}{C}-NH_2$$

Urea reacts with nitrous acid quantitatively according to the equation:

$$NH_2-\underset{\underset{O}{\|}}{C}-NH_2+2HNO_2 \longrightarrow 2N_2+CO_2+3H_2O$$

and is used to destroy excess nitrous acid in the reaction mixture.

When heated, urea parts with ammonia and is converted into **biuret:**

$$2NH_2-\underset{\underset{O}{\|}}{C}-NH_2 \longrightarrow NH_2-\underset{\underset{O}{\|}}{C}-NH-\underset{\underset{O}{\|}}{C}-NH_2+NH_3$$

As an amide, urea is hydrolysed both in acid and in alkaline medium:

$$NH_2-\underset{\underset{O}{\|}}{C}-NH_2 \xrightarrow{H_2O} 2NH_3+CO_2$$

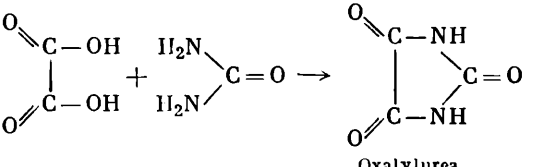
Urea is alkylated to give an alkylurea:

$$RI+NH_2-\underset{\underset{O}{\|}}{C}-NH_2 \longrightarrow RNH-\underset{\underset{O}{\|}}{C}-NH_2+HI$$

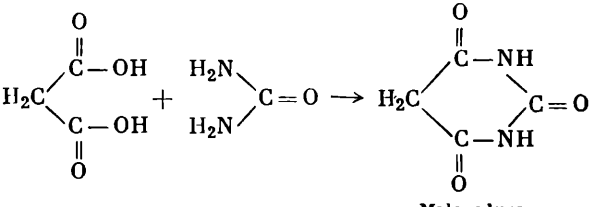
and is acylated to give the so-called **ureides:**

$$R-\underset{\underset{O}{\|}}{C}-Cl+NH_2-\underset{\underset{O}{\|}}{C}-NH_2 \longrightarrow R-\underset{\underset{O}{\|}}{C}-NH-\underset{\underset{O}{\|}}{C}-NH_2+HCl$$

Cyclic ureides are formed from dibasic acids:



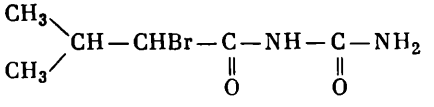
Oxalylurea
(parabanic acid)



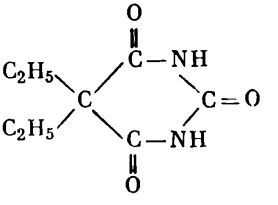
Malonylurea
(barbituric acid)

These compounds are heterocycles and are used in the synthesis, say, of purines (see Volume IV, "Heterocyclic Compounds").

The ureide of α-bromoisovaleric acid, known under the trade name **Bromural** (α-bromoisovalerylurea), is used as a sedative and hypnotic. The same effect is produced by Veronal (a trademark for barbital, diethylbarbituric acid).

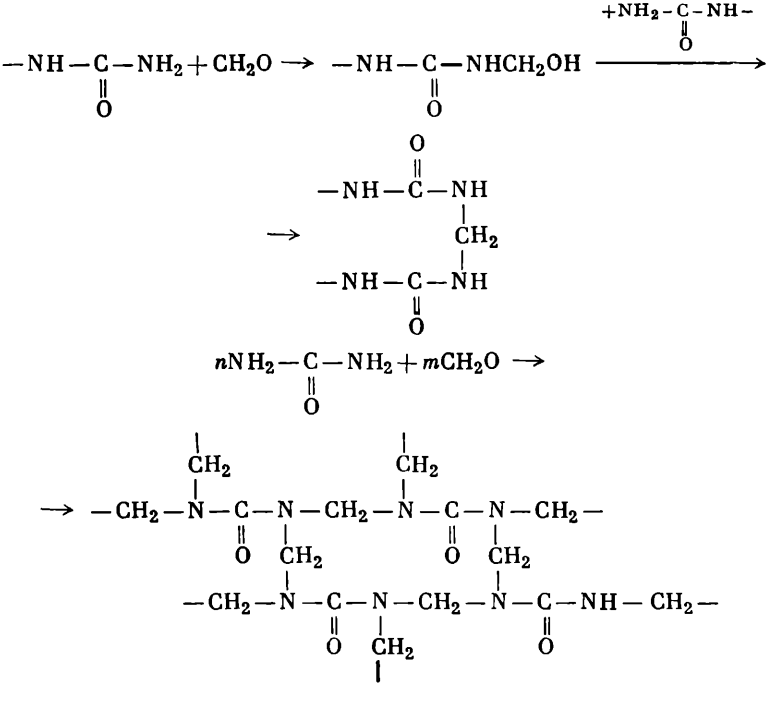


Bromural



Veronal

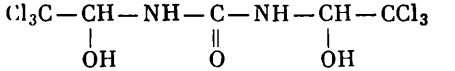
Urea finds wide application. With formalin, urea forms urea-formaldehyde resins which are widely used in the manufacture of plastics (aminoplasts) and adhesives. The molecules of urea are crosslinked by methylene bridges into macromolecules, methylol groupings being formed as intermediates, capable of being then converted into methylene bridges:



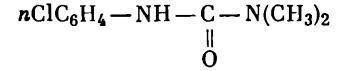
Urea is used as a non-protein feed supplement for sheep and cattle since the bacterial flora of their stomach is capable, due to the presence of the nitrogen of urea, of producing proteins that are assimilated by the animal.

Urea is an effective supplier of nitrogen to the soil and is widely employed as a fertilizer because it is readily hydrolysed.

Some of the derivatives of urea serve as herbicides. Examples are the products of condensation of chloral with urea: dichloralurea and monurone (N-4-chlorophenyl-N',N'-dimethylurea), etc.:

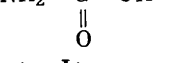


Dichloralurea

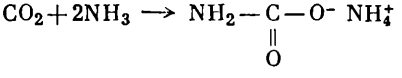


Monurone

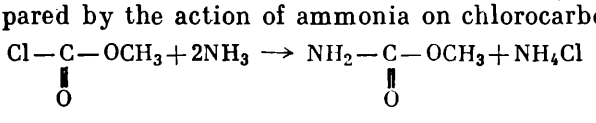
The amide of carbonic acid, **carbamic acid**,



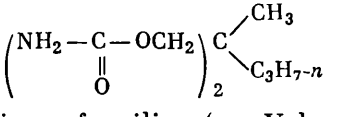
does not exist in the free state. Its ammonium salt is formed by the combination of CO_2 and NH_3 at room temperature and atmospheric pressure:



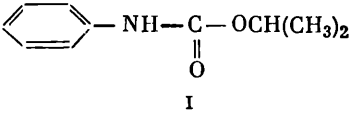
The esters of carbamic acid are called **urethanes** (*urethans*) and can be prepared by the action of ammonia on chlorocarbonic esters:



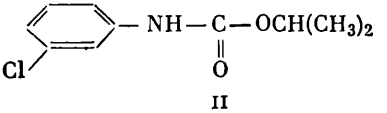
Some urethanes are used as tranquilizers, say, meprobamate



Urethanes, derivatives of aniline (see Volume III), are used as herbicides of selective action for "weeding" sugar beet, cabbages, cotton. Examples are phenylisopropyl carbamate (I) and chlorophenylisopropyl carbamate (II):



I

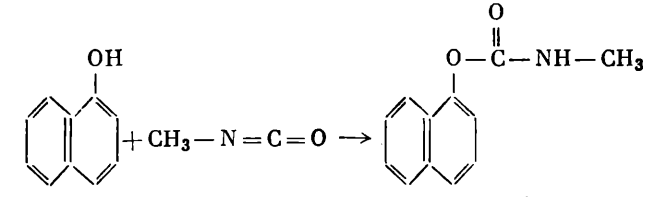


II

Methylurethane, which is the product of esterification of α-naphthol by methylcarbamic acid, is known under the trade name **Sevin** (1-naphthyl-N-methylcarbamate) and is used as an effective insecti-

cide, which undergoes hydrolysis relatively rapidly and is therefore less hazardous than chloro-organic insecticides.

Sevin is made by the following reaction:



α-Naphthol Methyl isocyanate α-Naphthyl-N-methyl carbamate (Sevin)

N-substituted urethanes can be synthesized from a chlorocarbonic ester and an amine. For example, with methylamine there is obtained **methylurethane:**

$$Cl-\underset{\underset{O}{\|}}{C}-OCH_3 + 2NH_2CH_3 \longrightarrow CH_3-NH-\underset{\underset{O}{\|}}{C}-OCH_3 + CH_3\overset{+}{N}H_3\ Cl^-$$

which usually serves as a starting material in the synthesis of diazomethane:

$$CH_3-\underset{\underset{H}{|}}{N}-\underset{\underset{O}{\|}}{C}-OCH_3 + HNO_2 \longrightarrow CH_3-\underset{\underset{O=N}{|}}{N}-\underset{\underset{O}{\|}}{C}-OCH_3 + H_2$$

Nitrosomethylurethane

$$CH_3-\underset{\underset{O=N}{|}}{N}-\underset{\underset{O}{\|}}{C}-OCH_3 + 2NaOH \longrightarrow CH_3-NH-NO + Na_2CO_3 + CH_3OH$$

$$CH_3-N=N-OH \xrightarrow[-H_2O]{} CH_2=\overset{+}{N}=\bar{N}$$

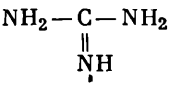
Diazomethane

Carbodiimides, which are compounds of the general formula R—N=C=N—R, in particular dicyclohexylcarbodiimide, have assumed great importance as substances that make two different molecules to form an anhydride (through fusion), say, two amino acids are fused into a peptide (see page 179). In this process, carbodiimides are converted into the corresponding ureas.

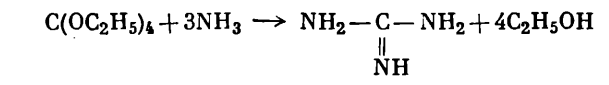
Carbodiimides can be obtained from the corresponding disubstituted ureas by the action of bromine and triphenylphosphine through the agency of triethylamine:

$$RHN-\underset{\underset{O}{\|}}{C}-NHR + Br_2 + (C_6H_5)_3P \xrightarrow{N(C_2H_5)_3} RN=C=NR + (C_6H_5)_3PO + 2HBr$$

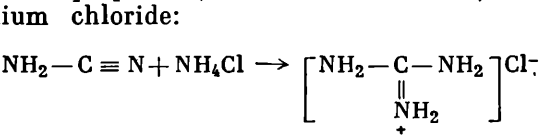
Guanidine which has the formula



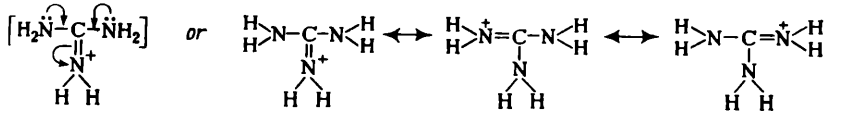
is made from an orthocarbonic ester by the action of ammonia:



It can also be prepared (in the form of a salt) from cyanamide and ammonium chloride:

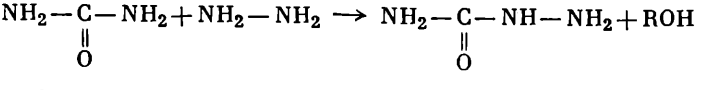


Guanidine is one of the strongest bases in organic chemistry (in contrast to urea which is only feebly basic). This is accounted for by the symmetry of the salt and by the usual lowering of the energy of the molecule in the mesomeric charge distribution, which is especially complete in the symmetrical molecule:

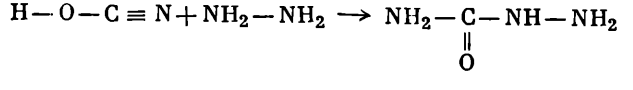


Guanidine binds even weak acids such as carbonic acid.

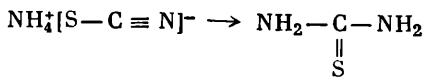
Semicarbazide, $NH_2—CO—NH—NH_2$, an important reagent for the detection of aldehydes and ketones (see Volume I), may be regarded as the hydrazide of carbamic acid. It is produced by heating hydrazine with urea or urethanes:



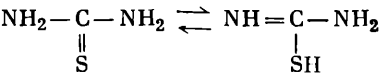
or through the action of a hydrazine salt on potassium cyanate:



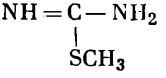
Thiourea, *thiocarbamide*, $NH_2—CS—NH_2$, is prepared by heating ammonium thiocyanate:



Thiourea is tautomeric and reacts also in the form of isothiourea:



For example, with methyl iodide it gives an S-methyl derivative

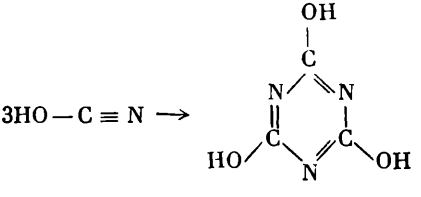


In a similar way, thiourea is alkylated even by ethers (Freidlina). Sulphonic acids react with thiourea to form characteristic **isothiouronic salts** which are utilized for their identification.

Thiourea is used for the synthesis of thiazole heterocycles (see Volume III).

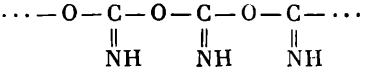
(d) *Nitriles of Carbonic Acid and Its Functional Derivatives*

Cyanic acid, HO—C≡N, which is unstable, immediately polymerizes above 150°C to **cyanuric acid** (2,4,6-trihydroxy-1,3,5-triazine):

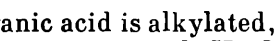


Cyanic acid Cyanuric acid

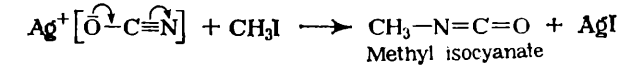
When heated up to a higher temperature, cyanuric acid depolymerizes, yielding liquid cyanic acid in the cooled receiver, which even at 0°C polymerizes rather rapidly to a linear polymer known as **cyamelide:**



The salts of cyanic acid are obtained by the oxidation of the salts of hydrocyanic acid; for example,



When the silver salt of cyanic acid is alkylated, an alkyl derivative ("an ester") of the isomeric **isocyanic acid**, H—N=C=O, is obtained, which does not exist in the free state:



Methyl isocyanate

that is, the alkylation of the anion of cyanic acid takes place at nitrogen and not at oxygen.

Isocyanates can be prepared by heating amines with phosgene:

$$3RNH_2 + COCl_2 \longrightarrow RN=C=O + 2R\overset{+}{N}H_3Cl^-$$

Isocyanates of the aromatic series are frequently utilized as reagents for the detection of alcohols, with which they form substituted urethanes:

$$R-N=C=O + R'OH \longrightarrow R-\underset{H}{N}-\underset{OR'}{C}=O$$

A reaction of this type (with a hydroxyl derivative of naphthalene) was given on page 24.

Aromatic urethanes are solid substances with characteristic melting points.

Isocyanates are hydrolysed by water to form amines:

$$R-N=C=O + H_2O \longrightarrow RNH_2 + CO_2$$

It was this reaction which led to the discovery of the amines by Wurtz.

With amines, isocyanates give substituted ureas:

$$R-N=C=O + NH_2R' \longrightarrow RNH-\underset{O}{C}-NHR'$$

At present, great industrial importance is attached to diisocyanates which can be obtained from the diamines of the aliphatic or aromatic series. With glycols and other dihydroxylic compounds the diisocyanates form high-molecular-weight polyurethanes:

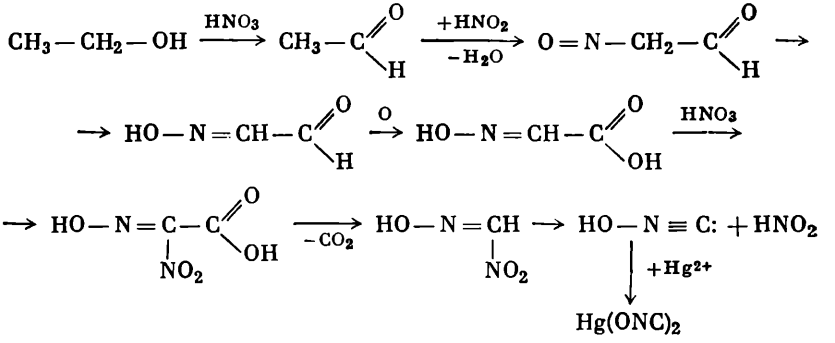
$$nO=C=N-R-N=C=O + nHO-Q-OH \longrightarrow$$

$$\longrightarrow O=C=N-R-\left(-\underset{H}{N}-\overset{O}{\overset{\|}{C}}-O-\right)_{n-1}-Q-OH$$

Polyurethanes, the world production of which in 1970 was 10^6 tons, have found application in the manufacture of high-quality tyres, foamed plastics of the various degrees of elasticity and rigidity, which are utilized in the production of furniture, car seats, heat-insulating materials, etc.

There is a third isomer of cyanic acid, which is known only in the form of a salt—**fulminic acid**, *carbonyl oxime*. It bears the same relation to cyanic acid as isonitrile to nitrile. Fulminic acid has the structure H—O—N≡C. The carbon atom in fulminic acid is in the same valence state as the carbon in isonitriles and carbon monoxide. The most important of its salts is **mercury fulminate**,

which is prepared by the action of nitric acid on metallic mercury in ethanol:



Mercury fulminate is still used occasionally at present as a detonator for explosives, though it has been largely replaced by the azides of less expensive metals.

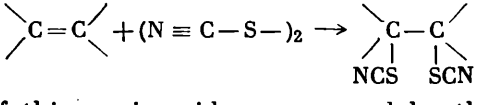
Thiocyanic acid, H—S—C≡N, is relatively stable. This is the nitrile of monothiocarbonic acid. Its salts are prepared by the addition of sulphur to salts of hydrocyanic acid:

$$KCN + S \longrightarrow K^+ {}^-S-C \equiv N$$

When acted on gently by halogens, thiocyanates give **thiocyanogen,** $(SCN)_2$, more exactly, **dithiocyanogen** (Zederbek):

$$2KSCN + Br_2 \longrightarrow N \equiv C-S-S-C \equiv N + 2KBr$$

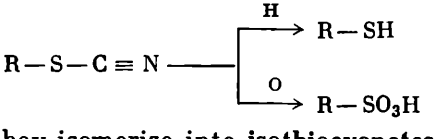
a pseudohalogen, which has many features in common with the halogens. For example, thiocyanogen adds on across the double bond:



The esters of thiocyanic acid are prepared by the alkylation of its salts:

$$KSCN + RI \longrightarrow R-S-C \equiv N + KI$$

The esters of thiocyanic acid when reduced form mercaptans, and when oxidized give sulphonic acids, which proves their structure:



When heated they isomerize into **isothiocyanates** which are structurally analogous to isocyanates:

$$R-S-C \equiv N \longrightarrow R-N=C=S$$

Isocyanates may also be obtained by a reaction that proves their structure:

$$2RNH_2 + CS_2 \longrightarrow \left[\begin{array}{c} R-N-C-\bar{S} \\ | \quad \| \\ H \quad S \end{array}\right][R-\overset{+}{N}H_3] \xrightarrow{HgSO_4}$$

$$\longrightarrow R-N=C=S + HgS + R\overset{+}{N}H_3\ HSO_4^-$$

The esters of iso- or pseudo-thiocyanic acid (isothiocyanates) are known as **mustard oils** since one of them, **allyl mustard oil** (*ordinary mustard oil*, the active principle of black mustard seed) is the product of the hydrolysis of the glucoside sinigrin contained in the seeds of black mustard (page 108). Synthetically, allyl mustard oil can be prepared in the following way:

$$CH_2=CH-CH_2Cl + KSCN \longrightarrow CH_2=CH-CH_2-S-C\equiv N + KCl$$

$$\downarrow \text{ heat}$$

$$CH_2=CH-CH_2-N=C=S$$

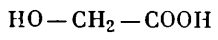
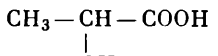
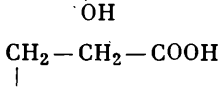
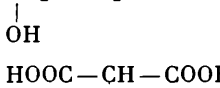
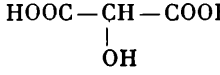
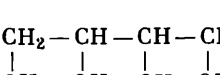
B. Hydroxy Acids—Homologues of Glycolic Acid

These hydroxy acids, in which the hydroxyl is contained not in the functional group, as is the case with carbonic acid, but in the hydrocarbon chain, are true alcoholic acids. Their names are derived from the names of carbonic acids with the prefix "hydroxy-" preceded by a numeral defining the position of the hydroxyl-bearing carbon atom (in the systematic nomenclature) or by a Greek letter meaning the same (α denoting the carbon atom adjacent to the carboxyl, β for the second, etc.). The physical properties and names of a number of monocarbonic monohydroxy acids, monocarbonic polyhydroxy acids, and polycarbonic mono- and polyhydroxy acids are given in Table 4.3. Many of the hydroxy acids have long been known (Scheele, the last quarter of the eighteenth century) as natural products, whose trivial names point to their origin: malic, lactic, tartaric, citric and other acids. Stereoisomerism is so characteristic of and so important to hydroxy acids that before we take up a systematic discussion of their synthesis and properties it is necessary to consider the problems of stereochemistry.

XI. Stereochemistry. Optical Isomerism I

We have already dealt with the isomerism of structurally identical compounds for the case of the geometrical isomerism (or cis-trans isomerism; see Volume I, pages 333 and 424) of compounds containing

TABLE 4.3.

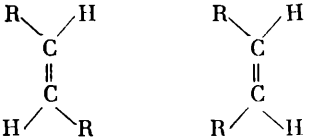
Formula	Name	m.p., °C
	Glycolic	63 (α) 79 (β)
	DL-Lactic	18
	D-Lactic	53
	L-Lactic	52.8
	Hydroacrylic or β-hydroxypropionic	—
	Tartronic or hydroxymalonic	158 (dec.)
	DL-Malic or hydroxysuccinic	130-131
	D-Malic	98-99
	L-Malic	100
	Racemic (anhydrous)	204-206
	D-Tartaric	170
	L-Tartaric	—
	Mesotartaric (anhydrous)	140
	Citric (anhydrous)	153
	D-Gluconic	132
	D-Mannonic	151
	D-Galactonic	95-100
	D-Saccharic or glucaric	125-126 (dec.)
	Galactaric or mucic	213-214

* Decomposes at 15 mm Hg.

Hydroxy Acids

h.p., °C	Dissociation constant in water at 25°C		Specific rotation, $[\alpha]_D^{20}$ in H_2O
	K_{a1}	K_{a2}	
Dec.	1.48×10^{-4}	—	
122*	1.39×10^{-4}		
Dec.	8.40×10^{-4} (at 100°C)	—	−2.26°
119*	—	—	+1.69°
Dec.	—	—	
110-120 (dec., subl.)	5×10^{-3}	—	—
150 (dec.)	3.9×10^{-4}	9×10^{-6}	—
—	—	—	+2.3°
140 (dec.)	—	—	−2.3°
—	1.04×10^{-3}	4.55×10^{-5}	
Dec.	1.1×10^{-3}	6.9×10^{-5}	+12°
—	—	—	−12°
—	6.0×10^{-4}	1.53×10^{-5}	
Dec.	8.4×10^{-4} (at 18°C)	1.8×10^{-5} (at 18°C) 4.0×10^{-6} (3H)	—
125-126	—	—	−6.7° → +12°
—	—	—	—
140-141	—	—	−11.2° → −57.6°
—	1.0×10^{-5}	—	+6.8° → +20.6°
—	—	—	—

a double bond, which can exist in two forms:



trans- *cis-*

Geometrical isomerism is a partial case of stereoisomerism. Another type of stereoisomerism is **optical isomerism,** which was first discovered by Louis Pasteur (1848) on stereoisomeric tartaric acids and interpreted later by van't Hoff and Le Bel (1871).

The facts are as follows. Substances that have a saturated carbon atom attached to four different substituent groups (such a carbon atom is called an **asymmetric carbon atom** or an **asymmetric centre**) exist in two structurally identical stereoisomeric forms. Such stereoisomers are identical in all their physical and chemical properties and differ only in two respects.

1. They crystallize in forms which have no plane of symmetry and are related as object to mirror image. It is exactly this property that allowed Pasteur to discover the phenomenon of optical isomerism: on crystallization of tartaric acid Pasteur detected visually the presence of two types of crystals; he separated them with the aid of forceps and thus isolated pure stereoisomeric tartaric acids.

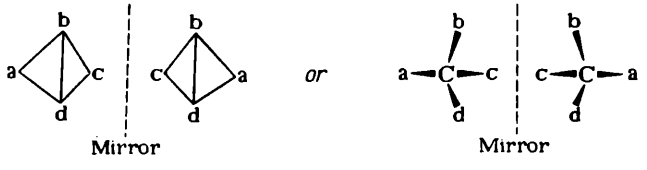
2. The two stereoisomers act differently on polarized light.

In a ray of light the oscillations of electrical and magnetic vectors are known to take place in mutually perpendicular planes which are also perpendicular to the direction of the ray. In polarized light, the oscillations of electrical and magnetic vectors occur within a single fixed plane for each rather than in the randomly changing, mutually perpendicular planes. When a ray of polarized light is passed through an "optically active" medium, the plane of polarized light is rotated (around the ray axis) to an angle proportional to the length of the layer of the optically active substance. In a crystal, the optical activity may depend on the asymmetry of its structure (such are, for example, the levorotatory and dextrorotatory modifications of quartz, SiO_2). In liquid and gaseous phases, the only factor responsible for the rotation of the plane of polarized light is molecular asymmetry. Stereoisomers known as **enantiomers** or **optical** antipodes* rotate the plane of polarization to the same angle but in different directions (to the left and to the right) under the same conditions—the solution concentration, the solvent, the wavelength and the pathlength of the ray being the same. The angles

* The less frequently used terms are *enantiostereoisomers* or *enantiomorphs.*—*Tr.*

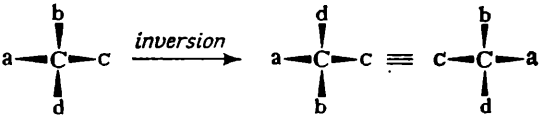
of rotation of the polarization plane are measured by means of a polarimeter.

The factor responsible for optical stereoisomerism is associated with the arrangement of the four different substituent groups linked to a carbon atom in the first valence state, i.e., to a saturated carbon atom, at the summits of a regular tetrahedron (the arrangement of atoms in space, responsible for the presence of stereoisomerism, is called the **configuration**). Such a geometrical figure has no plane of symmetry (a plane which divides an object symmetrically into two mirror-image halves). The reflection in the mirror of an object which has no plane of symmetry is not identical to the object and is its mirror-image antipode (enantiomer). For example, the mirror image of the human body is not identical to the original because it is a left-handed object. The left part of the man is reflected in the mirror as the right part, and vice versa. In the same way, the mirror image of an asymmetric molecule has a different, antipode arrangement of the substituent groups around the asymmetric carbon atom*:



The terms "an asymmetric molecule" and "an asymmetric atom" are sometimes replaced at present by the terms "a chiral molecule" and "a chiral atom" in order to avoid confusion because the term "asymmetric" may be thought to mean the absolute absence of any elements of symmetry in a molecule.

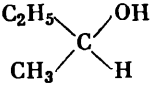
It should be stressed that the substituent groups in each of the enantiomeric molecules are at an equal distance from one another and their mutual influence is the same. Hence the identity of their physicochemical properties. It is easy to see, particularly on a model**, that when two substituents at an asymmetric carbon atom exchange their places, this leads to inversion—the formation of an antipode (enantiomeric) configuration:



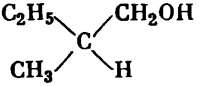
* In such perspective representations of the molecule the thickened end of the valency line rises above the plane of the paper and the pointed end is directed to this plane.

** Such a ball-and-stick model can be made from balls of crumpled brown bread and match-sticks.

We have already met with substances containing an asymmetric carbon atom. Such were, for example, normal secondary butyl alcohol (2-butanol) and "active" fermentation amyl alcohol (2-methyl-1-butanol):



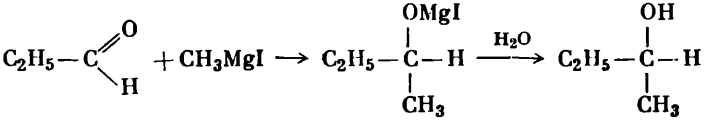
2-Butanol



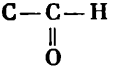
2-Methyl-1-butanol

In all similar cases there may be two kinds of arrangement of substituents around the asymmetric carbon atom: the left- and the right-handed configuration. The fermentation amyl alcohol of the structure given above, for example, is optically active and rotates the plane of polarized light to the left. Its specific rotation is $[\alpha]_D^{20} = -5.90°$.

In syntheses, which involve the formation of an asymmetric carbon atom in the molecule, the probability of formation of the left- and the right-handed configuration is the same, and the number of molecules of both configurations is the same. Such a mixture, naturally, does not rotate the plane of polarization: it is "optically inactive". For example, the asymmetry of a carbon atom, which was originally a carbonyl carbon atom, arises in the act of addition of a Grignard reagent to an aldehyde:



Since a methyl group adds on to the flat (a carbon atom in the second valence state) fragment of the molecule



then, when it adds on from above the plane of the paper, a configuration is obtained, which is different from the one that develops when a methyl group adds on from behind (or below) the paper, the two configurations being equally probable.

An equimolecular mixture of two antipodes is always capable of forming (within a definite temperature range) crystals in which right-handed and left-handed molecules are packed in a strict alternation. Such crystals differ in properties from crystals having only a left-handed or a right-handed configuration and are termed **racemates** or **racemic compounds.** It is obvious that they do not have

a configuration of their own. Since, however, the distance between any two groups in neighbouring molecules when only left-handed molecules or only right-handed molecules are packed into a crystal will inevitably differ from the distance between the same groups when the left and right molecules are packed together, then the forces binding the molecules in the crystal will also be different for the racemate, on the one hand, and for the left- and the right-handed configuration, on the other. Therefore, the racemate melts at a different temperature (above or below) than the levo or dextro

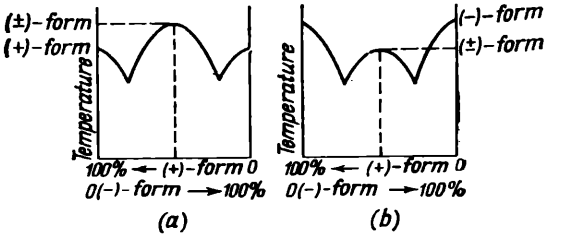


Fig. 4.1.
Melting-point diagrams for racemates:
(a) curve with a maximum melting point; (b) curve with a minimum melting point.

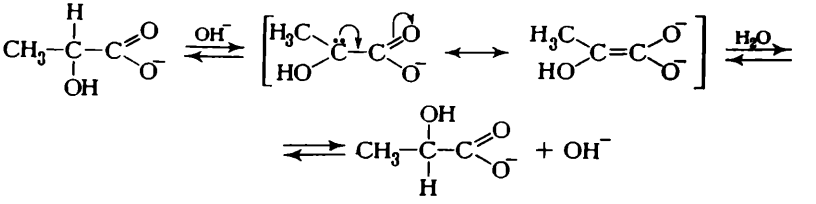
form, its solubility is different, and its crystals will possess a higher symmetry (for example, a plane of symmetry), etc.

Typical melting-point diagrams for racemates, levo (—)- and dextro (+)-forms and their mixtures are presented in Fig. 4.1.

Beyond the temperature ranges of existence of a racemate, crystals of the levo and dextro forms crystallize from solution separately (the Pasteur experiment on separation of crystals by means of tweezers).

The stability of configurations for different compounds is quite different, but in general the configuration is no less stable than the structure.

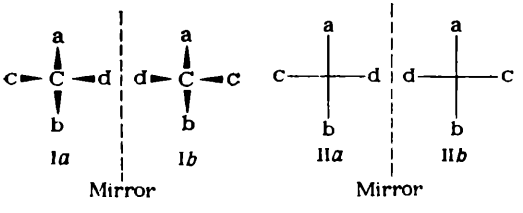
The process of conversion of an optically active enantiomer into a racemate is called **racemization**; under the conditions of conversion, say, of a levorotatory enantiomorph into a dextrorotatory one, the latter is of course transformed into the levorotatory form again, and equilibrium will be reached when the mixture contains equal amounts of the two enantiomers. Readily racemizable compounds are those which have an asymmetric carbon atom in the alpha-position to the carbonyl or carboxyl group or in general to an electrophilic substituent provided that the asymmetric carbon atom carries a hydrogen atom. This is accounted for by the fact that hydrogen is easily replaceable. Therefore, in particular, α-hydroxy acids are racemized relatively readily when boiled with alkalis:



What configurations rotate the plane of polarization to the right and what to the left? No general answer can be given to this question for the simple reason that some substances change the sign of rotation upon change of the solvent and sometimes even when the concentration of the solution is also changed.

A question may legitimately be raised as to an **absolute configuration** for each given pair of antipodes, but chemical methods can only provide information on the **relative configuration**, i.e., can make it possible to establish a series of compounds of one configuration by the chemical transformation of some substances of this series into others. In this process, the chemical bonds with an asymmetric carbon atom must be left untouched, otherwise this would lead to a change of the configuration to an enantiomorphic one (see Walden inversion, page 50). But once the absolute configuration of any one compound in the series is established, the absolute configurations of all the remaining compounds will also be known. Such determinations of absolute configurations have been accomplished by means of X-ray structure analysis of crystals, so that the absolute configurations of many stereoisomeric substances are known at present. Before this became possible, there had been arbitrarily chosen a reference configuration—the configuration of glyceraldehyde taken as an arbitrary standard. The guess has proved to be the correct one.

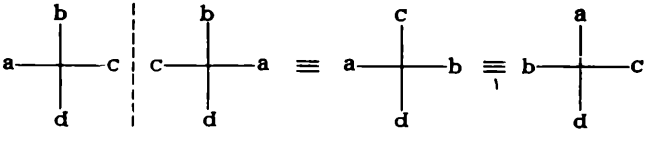
Fischer Projections. In order to ascertain the relations between the relative configuration and the absolute configuration, it is necessary first to consider the planar representation (in two dimensions) of stereochemical formulas which have a three-dimensional sense. Two methods of representation are described here. The one on the left (formulas I*a* and I*b*) is in essence a perspective drawing which is little applicable to cases with many asymmetric atoms; the others on the right are the Fischer projection formulas (II*a* and II*b*):



Both pairs of formulas correspond to each other. In formulas I*a* and I*b*, the east and west bonds of the asymmetric carbon atom are considered to extend out of the plane of the paper, and the north and south bonds extend behind the plane of the paper. In the Fischer projection the three-dimensional model of the molecule is above the projection plane and in such a manner that the groups written to the left and right of the asymmetric carbon atom are projected from above the plane of the page and the groups written above and below the central atom are projected from beneath the plane. This is evidenced by the correspondence between the formulas in the pairs I*a*-II*a* and I*b*-II*b*. In order to show that a projection formula is meant, the symbol C for the asymmetric carbon atoms is omitted (this rule is not always followed), meaning that it is at the intersection of the horizontal and vertical lines.

In using Fischer models one must know certain rules.

1. Fischer models may not be taken out of the plane. The rotation by 180° with withdrawal of the Fischer projection out of the plane leads to the projection of the antipode:

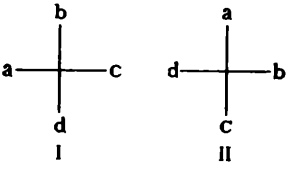


2. Fischer projection formulas can be rotated in the plane only by 180°.

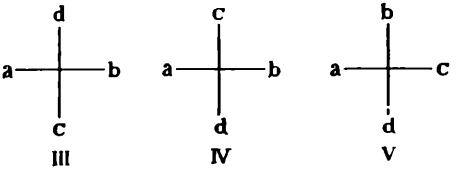
3. In Fischer models one may interchange, clockwise or counterclockwise, three substituents at the same asymmetric carbon atom.

4. The interchange, in the Fischer projection formula, of any two substituents (and hence any odd number of such interchanges), just as in the real molecule, leads to the formula of an antipode. An even number of such transformations does not change the significance of the formula. This rule is valid for both three-dimensional models and projection formulas.

A confusion may be caused by rule 2 only. Let us explain it: turn the original projection by 90°, which is prohibited by rule 2, and you will obtain projection II from projection I:



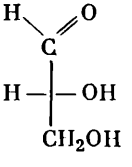
Let us now interchange in the resulting projection II the substituents *a* and *d* (projection III); then *d* and *c* are interchanged (projection IV) and, finally, *c* and *b* are interchanged (projection V):



Thus, by way of an odd (threefold) number of pair transpositions we have obtained the original configuration I. Incidentally, if configuration II were identical to I, we must have arrived at the enantiomorphic configuration (rule 4). Hence, projection II is an enantiomorphic projection (an antipode with respect to I) and the rotation by 90° changes the configuration. It is natural that the rotation by 180° (in the plane of the drawing) leaves the configuration unchanged.

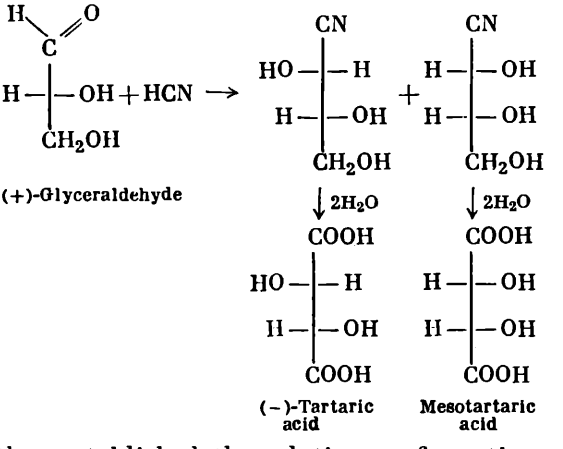
(A) Relative and Absolute Configurations

Let us return to the problem of the relative and absolute configurations. The first is more important. M. A. Rosanoff and Wohl proposed that glyceraldehyde, $CH_2OH—CHOH—CHO$, be used as a reference substance for establishing the relative configurations of other compounds. Fischer assigned the following configuration to dextrorotatory glyceraldehyde which is designated as (+)-glyceraldehyde:

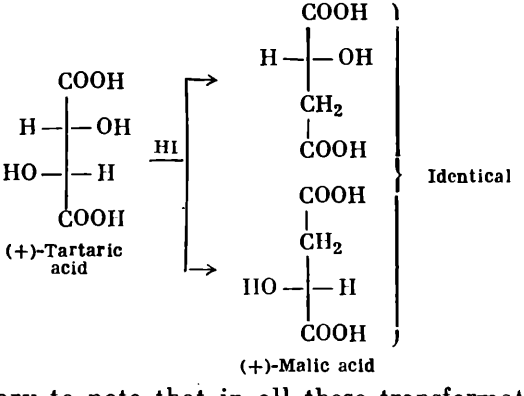


It was important to establish the relationship between the configuration of this compound and other standard substances: (+)- and (—)-malic acid, $HOOC—CHOH—CH_2—COOH$, and (+)- and (—)-tartaric acid, $HOOC—CHOH—CHOH—COOH$. As evidenced by experiments, the cyanohydrin synthesis (see Volume I, page 176) changes (+)-glyceraldehyde into a mixture of nitriles of (—)-tartaric acid and a so-called mesotartaric acid, which is inactive because of the symmetry of the molecule (mesotartaric acid will be considered later). The hydrolysis of the nitriles followed by the oxidation

of the CH_2OH group yields the acids indicated above:



We have thus established the relative configurations of (+)-glyceraldehyde and (—)-tartaric acid.* Since the reduction of (+)-tartaric acid by HI gives (+)-malic acid, it follows that the relative configurations of these acids are also established:



It is necessary to note that in all these transformations none of the bonds of the central asymmetric carbon atom (the one whose configuration is considered) is broken.

The relative configurations of other compounds are established in a similar way with respect to one of the three substances indicated.

Application of the methods of X-ray analysis has also established the absolute configuration of the rubidium salt of the two optically active tartaric acids and, hence, the absolute configurations of all

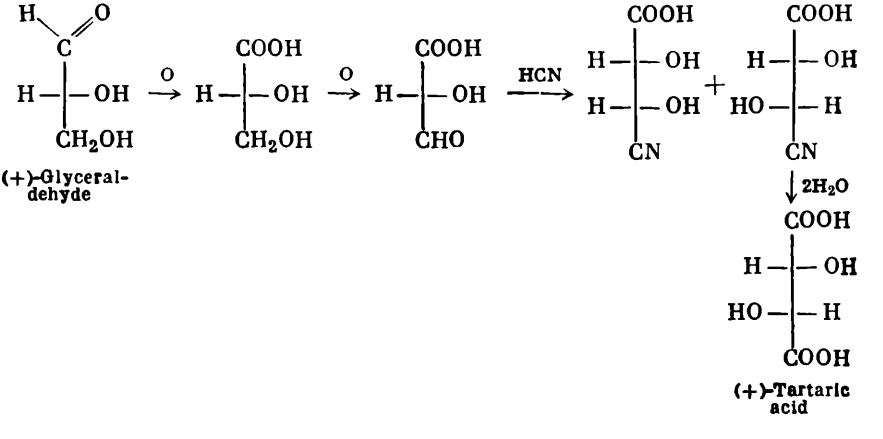
* It is this acid which is contained in grape juice and in tartar or argol—the acid potassium salt that separates during fermentation in hard brown crusts in the wine vats and storage tubs.

substances whose configurations relative to tartaric acids were known, including the configuration of glyceraldehydes. Fischer's arbitrary choice has thus been proved as the correct one (the choice had a 50 per cent chance of being correct)!

The signs (+) and (—), as has been said above, indicate the direction of rotation of the plane of polarized light. In the older literature, the letters *d* (*dexter*) and *l* (*laevus*) were used for the dextrorotatory and the levorotatory form, respectively. Later the meaning of these designations changed. The letter D is now used to specify, irrespective of the sign of rotation, the same relative configuration as that of (+)-glyceraldehyde, and the letter L indicates the enantiomorphic configuration. Thus, the letters D and L are the configurational family signs.

If D-(+)-glyceraldehyde is assumed to be the parent compound, the above series of transformations, which relates it to (—)-tartaric acid and (—)-malic acid, must lead to the assignment of the letter D to these acids. This convention would be inconvenient since for two parent compounds at least it would be important to preserve the unified conventions (as to the sign of rotation and to the configurational family sign). This would also be in agreement with the historically established convention according to which (+)-tartaric acid is designated as D-tartaric acid and (+)-malic acid as D-malic acid. By the way, the configurational relations and the corresponding designations D and L are very important (and persistent) for a long series of similar compounds which are related to one another by conversions of the same type. An illustration of this will be given later (sugars) and the usefulness of the designations D and L (irrespective of the sign of rotation) will be obvious.

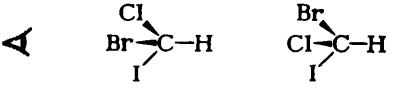
That these designations are conventional may be demonstrated by establishing, for example, a genetic relation between (+)-tartaric acid and (+)-glyceraldehyde and not (—)-glyceraldehyde:



Thus, in this case (+)-tartaric acid must be classified as belonging to the D-series and (+)-malic acid must be regarded as D-malic acid because of its genetic relation to (+)-tartaric acid. It is this convention, which is in keeping with the historical tradition, that is selected.

The convention just indicated has made it necessary, in certain cases, to use subscripts for D and L for more definiteness, say, D_G, D_R, D_S (or L_G, L_R, L_S), where G stands for glyceraldehyde, R for lactic acid, S for serine (hydroxyamino acid). Thus, the symbol L_S means that the configuration is identical with the configuration of levorotatory serine (page 160).

Hence, any of the above symbols signifies only the configuration relative to this or that reference compound. But since any relative configuration can be brought to the absolute one, we should adopt such a designation for the absolute configuration which would be free from the uncertainty of the designations D and L explained above. Such a system for specifying absolute configuration was proposed by Cahn, Ingold and Prelog and is known as the **Sequence Rule.** It consists in the following: the four atoms attached directly to the asymmetric carbon atom are arranged in order of decreasing atomic number. For example, for CHClBrI the sequence is I > > Br > Cl > H, and the molecule is arranged in such a manner that the atom with the lowest atomic number (H in this case) is pointing away from the eye of the viewer:

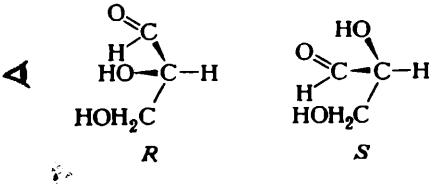


A *B*

The remaining three substituents may be arranged in the molecule so that their atomic numbers decrease in a clockwise direction (from the standpoint of the viewer) as in *A*, which is said to have the *R*-configuration. The molecule is assigned the *S*-configuration if the substituents lie in a counterclockwise sequence. The symbols *R* and *S* are taken from the Latin words, *rectus* and *sinister*, meaning right and left, respectively.

If two or more of the atoms of the first set (first atoms, i.e., atoms attached directly to the asymmetric carbon atom) have the same atomic number (for instance, if two, three or all four atoms are carbon atoms), the priority order is determined by the atoms attached to these (second set), namely by the sum of the atomic numbers of the second atoms. If the atom attached to the asymmetric carbon atom is bound to other atoms by a double or triple bond, the atom at the end of the multiple bond is counted twice (double bond) or three

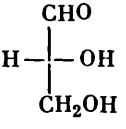
times (triple bond). For example, the carbonyl oxygen is assumed to have an atomic number of 16 and not 8 as the hydroxyl oxygen. Let us illustrate this by the example of glyceraldehyde:



R *S*

Here the combined atomic numbers of the second atoms are as follows: $CH_2OH = 8 + 1 + 1 = 10$, $CHO = 16 + 1 = 17$, and all the substituents around the asymmetric carbon atom are arranged in the following sequence of decreasing priority: OH (8 for the first oxygen) > CHO (6 for the first atom and 17 for the second atoms) > > CH_2OH (6 for the first atom, 10 for the second set) > H (1 for the first atom).

Thus, the configuration of glyceraldehyde in the left-hand formula is the *R*-configuration, and the enantiomorphic isomer of glyceraldehyde (on the right) has the *S*-configuration. It is easy to see that in the Fischer projection the *R*-configuration will be represented as follows:



that is, for the given reference compound the symbols *R* and D (and, accordingly *S* and L for the antipode) coincide*.

Of course, such coincidence is not accidental because the Cahn-Ingold-Prelog rules were worked out so as to provide this coincidence for the reference compound. It is absolutely clear that the coincidence or non-coincidence between the symbols *R* and D (and, accordingly, between *S* and L) is a matter of chance for all other compounds. Thus, while being used as the notation for absolute configuration, the symbols *R* and *S* cease to denote the configurational assignments. Since the family sign is usually important, the symbols D and L are still used for the purpose.

A. P. Terent'ev, V. M. Potapov, A. M. Zuckerman and A. N. Kost have devised a system of notation of absolute configuration which may be related to any system of nomenclature, for example, to the IUPAC or trivial system. According to their system, the antipode

* It is to be emphasized that in projecting a molecule according to Fischer it is required that the top and bottom atoms attached to the asymmetric carbon atom be disposed behind the plane of the paper and the remaining two, which are projected on to a horizontal line, be placed in front of this plane.

configurations are denoted by the Greek letters ρ and σ. A Fischer projection formula is drawn, the main chain being placed vertically and the usual system of numbering the atoms being used. The asymmetric carbon atom thus assumes the number *n*. If* the substituent X is on the left of the asymmetric carbon atom (and the substituent Y on the right), then the compound is designated as an *n*ρ-X-[name of compound] or as an *n*σ-Y-[name of compound]. Both notations are correct. The antipodes of these compounds are accordingly written as *n*σ-X-[name of compound] and *n*ρ-Y-[name of compound]. Let us illustrate this by an example:

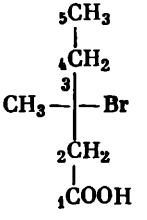
3-Bromo-3ρ-methylpentanoic acid

or

3σ-Bromo-3-methylpentanoic acid

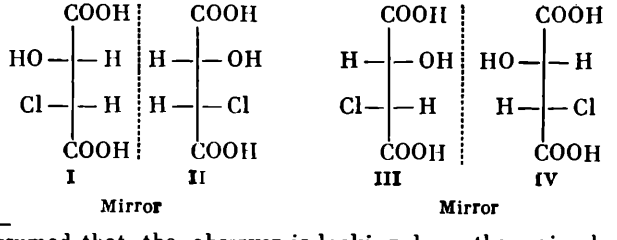
or

3σ-Bromovaleric acid



XII. Compounds with Two Asymmetric Carbon Atoms. Diastereoisomerism

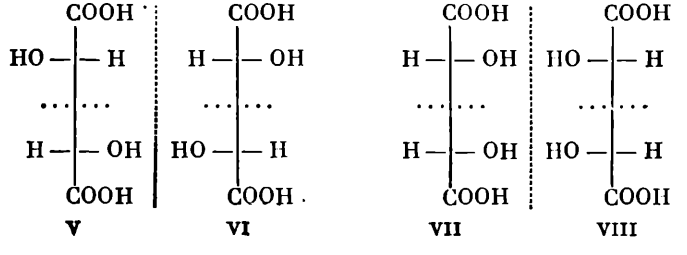
We have so far considered the stereochemistry of compounds with one asymmetric carbon atom. The only exception was tartaric acids containing two asymmetric carbon atoms, but we have not fixed our attention on this circumstance. Let us now consider compounds with two or more asymmetric carbon atoms. It is easy to arrive at the conclusion that the number of stereoisomers (without racemates) increases to 4 if two asymmetric carbon atoms are present and to 2^n if there are *n* asymmetric carbon atoms. As an example, let us take chloromalic (hydroxychlorosuccinic) acids with two asymmetric carbon atoms and write all the possible configurations for them:



* It is assumed that the observer is looking down the main chain from the beginning of its enumeration.

All the four compounds are optically active since the molecules (and the projections) have no plane of symmetry (in projections the plane of the drawing is not regarded as a plane of symmetry for the obvious reason). They in pairs (I and II; III and IV) are enantiomers (antipodes) and all that has been said above is valid for these pairs as well. New relations that arise are: I to III and I to IV or II to III and II to IV. The compounds of each pair are not antipodes, but they are not identical either; they are stereoisomers. This relationship between nonenantiomeric stereoisomeric compounds, which are thus not mirror-image forms, is called **diastereoisomerism** and the stereoisomers are termed **diastereoisomers** or, more commonly, **diastereomers.** Unlike enantiomers, diastereomers differ in physical and chemical properties. This is understandable since in diastereomers the substituent groups cannot assume an arrangement such that all the substituents in both compounds are at the same distance from one another. And since the distances are different, it follows that their mutual influence will also be different; hence the difference in their constants.

An important special case is the identity of the substituents around two asymmetric carbon atoms. Let us illustrate this by the classical example of tartaric (dihydroxysuccinic) acids:



Inspection of the plane diagrams of molecules V-VIII shows that V and VI are enantiomorphs or optical antipodes, and VII and VIII are identical configurations, as can be seen by rotating one of them 180° in the plane of the page. Thus, one of the four configurations ($2^2 = 4$) is omitted and there remain three: two optical antipodes, V and VI, which represent L-(—)-tartaric acid and D-(+)-tartaric acid, respectively, and their diastereomer, mesotartaric acid. The configurations of the two asymmetric carbon atoms in L-(—)-tartaric acid (V) are identical; the same is true of D-(+)-tartaric acid (VI). Indeed, if we cut with a mirror (dotted line) the projections V and VI, we shall see that the lower half is not a mirror image of the upper one. Hence, the halves are identical since no third possibility exists. We may formulate this as follows: L-(—)-tartaric acid has a levo-levo configuration and D-(+)-tartaric acid has a dextro-dextro configuration. The situation is different with projection VII. The

mirror placed perpendicular to the plane of the projection of the carbon skeleton cuts it into mirror images. Thus, this is a levo-dextro configuration. The molecule is symmetrical (the plane of the mirror is the plane of symmetry), and its mirror image (projection VIII) is identical with the object. Therefore, mesotartaric acid (VIII) is optically inactive. Such symmetrical molecules, although they contain two asymmetric carbon atoms, are said to be optically inactive through **internal compensation** and are called *meso*-forms in accordance with mesotartaric acid. Later on, in the consideration of the stereochemistry of sugars we shall see that these *meso*-forms serve as reference standards for establishing the configurations of compounds with many asymmetric carbon atoms.

Table 4.4 lists the properties of tartaric acids: two optical antipodes—the dextrorotatory compound and its enantiomorphic levorotatory isomer, their racemate—racemic or (±)-tartaric acid, and mesotartaric acid. As seen, the difference in properties between the diastereomers is so great that they can be separated without difficulty if they are found to be in a mixture.

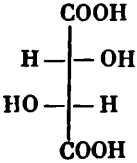
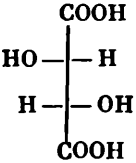
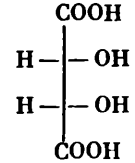
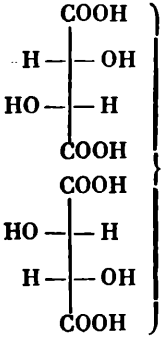
Racemic (paratartaric) acid is prepared by prolonged heating of D- or L-tartaric acid with water (racemization, page 35). Mesotartaric acid is also formed by this reaction, and heating with weak alkalis may convert any of the tartaric acids into mesotartaric acid. In this case, racemization alters the configuration of one of the asymmetric carbon atoms.

Resolution of Antipodes. Enantiomers or optical antipodes are always formed in equal amounts in syntheses and are identical in boiling and melting points, solubility and all other properties on which the separation of substances is based. But how can two optical antipodes be separated from each other? The process of separation of enantiomers is known as **resolution.** We have already said that the simplest way to achieve this was first employed by Pasteur who picked out by hand, using a pair of tweezers, the levorotatory and dextrorotatory crystals of D- and L-tartaric acids which were formed separately at a temperature beyond the range of existence of a racemate (below 27°C).

The second method is the biochemical method of resolution. Microorganisms are usually capable of consuming one of the two enantiomers, leaving the other untouched. Examples of such microorganisms are various species of mould. But, first, not every substance is "edible" for microorganisms, and, second, one of the enantiomers is destroyed.

The universal and widely used method of separation of enantiomers consists in the following: a racemate (or a racemic mixture) is allowed to react with an optically active form (either levo or dextro) of a compound capable of interacting with the racemate to be separated into its enantiomers. Such an optically active compound

TABLE 4.4. Tartaric, Racemic Tartaric and Mesotartaric Acids

Formula	Name	m.p., °C	b.p., °C	Dissociation constant in water at 25°C		$[\alpha]_D^{20}$ in water
				K_{a1}	K_{a2}	
	D-Tartaric acid	170	Dec.	1.1×10^{-3}	6.9×10^{-5}	+12°
	L-Tartaric acid	—	—	—	—	−12°
	Mesotartaric acid (anhydrous)	140	—	6.0×10^{-4}	1.53×10^{-5}	—
	(±)-Tartaric or racemic acid	205	—	1.20×10^{-3}	4.0×10^{-5}	—

is usually derived from a natural source. To resolve the racemates of amines (or other bases) and alcohols, use may be made, for example, of natural (from wine tartar) D-tartaric acid. The reaction with amines gives salts and with alcohols, esters. For the racemates of acids to be resolved, use is frequently made of alkaloids such as quinine or strychnine produced from plants in which they are present in an optically active form. The racemic mixture forms two diastereoisomers of a derivative with an optically active reagent. If we designate the optical antipodes of the compound to be resolved by the letters L and R, and the optically active reagent by L′, then both derivatives (salts, esters, etc.) will have the following symbols:

$$\begin{matrix} L & & R \\ L' & \text{and} & L' \end{matrix}$$

These two diastereomers possess different physical and chemical properties, say, different solubilities, and can be separated by one of the ordinary methods, say, by fractional crystallization. After separation, the optically active reagent is removed from the molecule (if the diastereomer is a salt, it is treated with acid or alkali, and if it is an ester, hydrolysis is carried out) and pure forms of enantiomers are isolated.

A method has recently been introduced for separation of enantiomers without converting them into diastereomers. The method is based on selective adsorption by natural asymmetric materials or on the use of an optically active solvent. Thus, for example, enantiomers may be separated by gas-liquid chromatography through the use of esters of optically active alcohols as the mobile phase.

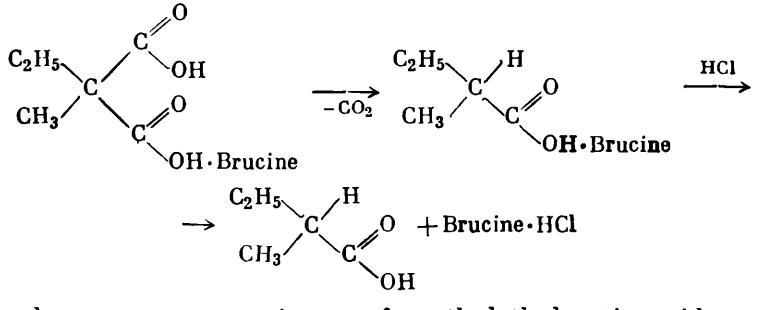
The resolution can also be effected by seeding (inoculating) a supersaturated solution of a racemate with crystals of one pure enantiomer to cause immediate crystallization of that enantiomer, leaving the other in solution.

Still another method of resolution has been proposed, which, however, has limited applicability: urea, whose molecule is symmetric, crystallizes in two enantiomorphic forms (like quartz). We have mentioned earlier clathrate compounds formed by urea and saturated normal hydrocarbons, which fill the empty vacancies in urea crystals. By using the levorotatory and dextrorotatory crystals of urea it is possible to separate the enantiomers of hydrocarbons provided that these hydrocarbons or their derivatives are capable of forming clathrates with urea, i.e., their molecules are close in size to normal hydrocarbons. In this way, E. I. Klabunovsky, V. V. Patrikeev, and A. A. Balandin effected the resolution of 3-methyloctane and 3-methylnonane into their enantiomers.

Asymmetric Synthesis. Since ordinary laboratory syntheses invariably produce a racemic mixture, there arises a question: How are pure enantiomorphs formed in living nature? In order to

answer this question, it should be recalled that all catalysts of biological origin (enzymes) without which no biochemical reaction is possible, are complex asymmetric molecules. Therefore, the transiently formed reaction complexes of the reacting molecule with a catalyst (enzyme) are diastereomers in character. This accounts for the fact that the action of enzymes is selective and that they synthesize only one of the two possible enantiomers.

Marckwald and McKenzie produced an asymmetric carbon by heating the acid salt of methylethylmalonic acid with the alkaloid brucine (a pure natural enantiomer) until the carboxyl is split off:

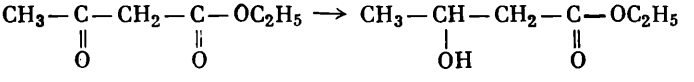


The levorotatory enantiomer of methylethylacetic acid predominated somewhat in the reaction product. The difference is that the action of enzymes is highly specific. The above question now assumes the following form: How did separate enantiomers first appear in living nature and in the mineral kingdom?

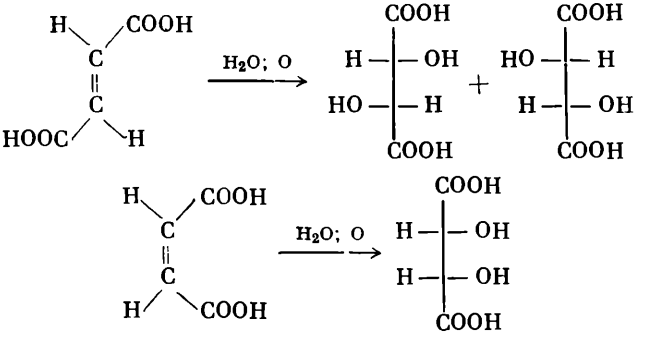
An answer to this question is provided by experiments known as **asymmetric synthesis** (*asymmetric induction*). In nature, there are two asymmetric factors capable of exerting a chemical action. First, circularly polarized rays of light. It is known that when reflected from the surface, say, of water, the light is partially polarized, or it can be polarized completely at a certain definite angle of incidence. Can polarized light induce chemical transformations leading to the formation of one of the enantiomers? The Czech scientist Byk came to the conclusion that it is possible. W. Kuhn and Braun accomplished an asymmetric synthesis through the decomposition of ethyl α-bromopropionate by circularly polarized light and observed the predominant formation of a small amount of a dextro- or levorotatory isomer (depending on whether it is right- or left-circularly polarized light). Tenn and Ackerman effected the reaction of hydrogen peroxide with an ester of fumaric acid and the reaction mixture was also irradiated with right-circularly polarized light; the product obtained was tartaric acid with a slight preponderance of the D-enantiomer (specific rotation $[\alpha]_D = = +0.073°$). The possibility of photochemical synthesis of enantiomers was thus proved.

Second, there are enantiomorphic forms of crystals in nature, say, of quartz. Schwabe succeeded, by applying nickel onto crystals of one of the modifications of quartz, in dehydrogenating normal secondary butyl alcohol to methyl ethyl ketone so that one of the enantiomers of the starting butanol predominated in the residue; true, the preponderance was slight in this case too and the mixture showed a low optical activity ($[\alpha]_D = +0.13°$). A. P. Terent'ev and E. I. Klabunovsky carried out the cyanoethylation (see Volume I, p. 413) of methylcyclohexanone over a catalyst (alkali applied onto crystals of dextrorotatory quartz). An optically active mixture was obtained, with a slight predominance of the dextrorotatory nitrile. Thus, the possibility of primary synthesis with a predominance of one of the enantiomers in the presence of asymmetric crystals as catalysts was also proved.

It is possible, as reported by Izumi, to hydrogenate acetoacetic ester to an optically active ester of β-hydroxybutyric acid with an optical yield of 27 per cent by using Raney nickel produced by treatment of the Ni/Na alloy with water containing an optically active acid, say, D-malic acid. The reaction proceeds as follows:



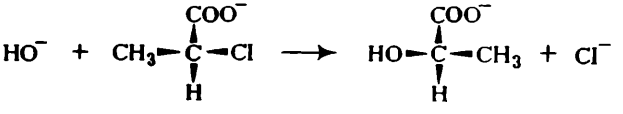
It is interesting to trace the relationship between *cis-trans*-isomers and optical isomers. It may be illustrated by the relation of maleic and fumaric acids to tartaric acids. It has been found that when permanganate is oxidized in water (Wagner reaction), fumaric acid forms a racemic mixture of the levorotatory and dextrorotatory tartaric acids, and maleic acid gives mesotartaric acid:



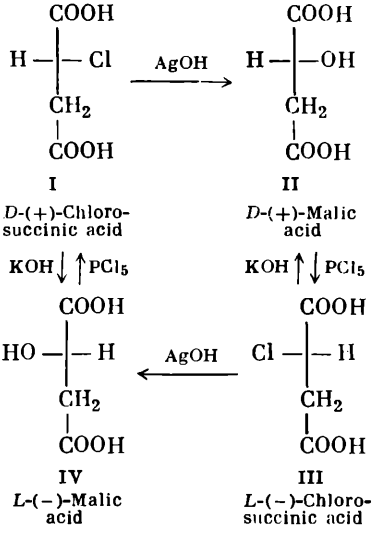
In the medium of optically active ethers, an asymmetric Grignard reagent adds on to asymmetric carbonyl compounds with the formation of optically active symmetric alcohols in an optical yield of up to 70 per cent.

The course of such reactions becomes clear by reference to the formulas and even better to the models. It is, however, only the Wagner oxidation that proceeds in the *cis*-position and may serve as a means of distinguishing between *cis*-isomers and *trans*-isomers by the optical activity of the addition product (of course, only after the racemate is resolved into optical antipodes) or by the inactivity and non-resolvability of the reaction product into its enantiomers. Other additions across the π-bond, say, the addition of a bromine molecule, take place in the *trans*-position. To understand this, it is necessary to know the so-called Walden inversion (or optical inversion), a phenomenon discovered by Walden in 1896 in Riga.

Walden Inversion. A nucleophilic substitution of the S_N2 type at an asymmetric carbon atom, where it is easily detected, and in fact at any saturated carbon atom, proceeds with a change in the configuration. Such a configurational change is known as an **optical inversion** or the **Walden inversion,** after its discoverer, Paul Walden. An example of the Walden inversion is

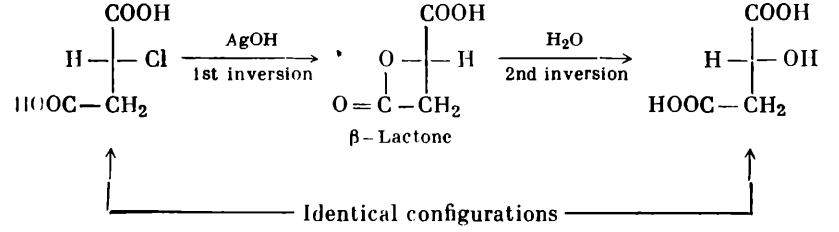


In this case, however, a Walden inversion could have been discovered if absolute configurations had been known, but in 1896 X-ray analysis was not available. Walden established the occurrence of optical inversion by carrying through the following cycle of transformations:

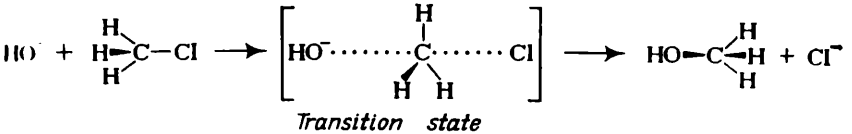


The absolute configurations were not known to Walden. He only observed the directions or signs of rotation. But the fact itself that a change (inversion) of configuration has taken place on the path I → II → III or II → III → IV is clear since by a two-stage process an optically active compound [(+)-chlorosuccinic acid (I) in the first case and (+)-malic acid (II) in the second] has been converted into its antipode. It means that one reaction proceeds with and the other without inversion of configuration.

More exactly, according to the hypothesis put forward by Hughes and Winstein, the second reaction proceeds with two inversions of configuration:



The reactions of bimolecular nucleophilic substitution at the asymmetric saturated carbon atom of course take place by the same mechanism: the nucleophilic substituent attacks from the side opposite to that of the atom being replaced; in the transition state the other groups attached to the asymmetric carbon atom are pulled into a plane which contains that carbon atom and the bonds may be thought of as the spokes of an umbrella being turned inside out in changing to the final product:

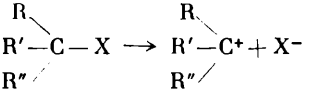


Transition state

The Walden inversion is a rule for nucleophilic substitution reactions which proceed as second-order reactions (S_N2). The only exception is believed to be reactions with participation of the neighbouring atom, like the above reaction involving the intermediate cyclization into lactone.

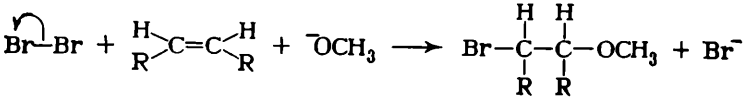
This is, however, an exception only in the sense that the final reaction product isolated has the same configuration as the starting material. In actual fact, such reactions involve two Walden inversions and, hence, serve as a confirmation of rather than an exception to the general rule.

Nucleophilic substitution reactions of the first order (S_N1) take place with a preliminary dissociation of the starting compound into a cation and an anion:

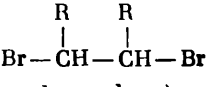


and, in principle, must result in racemization since the cation must assume a flat configuration and the nucleophile that displaces X may attack it either from the right or from the left. In fact, racemization is sometimes partial since the cation does not always have time to flatten before the attack, and the anion X^- does not always have time to break away sufficiently far and shields one side of the plane. (Occasionally, the solvent also takes part in the shielding.)

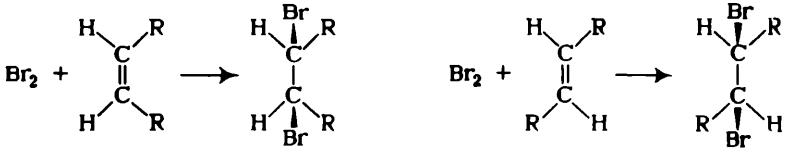
Addition to Olefins (*Trans-* and *Cis-*). At this point it is most convenient to consider also the stereochemical course of the reaction of addition of halogen across the olefinic double bond. We have already seen (Volume I, page 335) that this is a heterolytic reaction and the attack begins with electrophilic addition of one halogen atom. This is supported by the fact that the following reaction occurs in a medium containing an excess of other anions, say, CH_3O^-:



The second halogen atom (or any other anion, as CH_3O^- in this particular case) adds on in such a manner that the *cis*-olefin gives a racemate of an optically active product



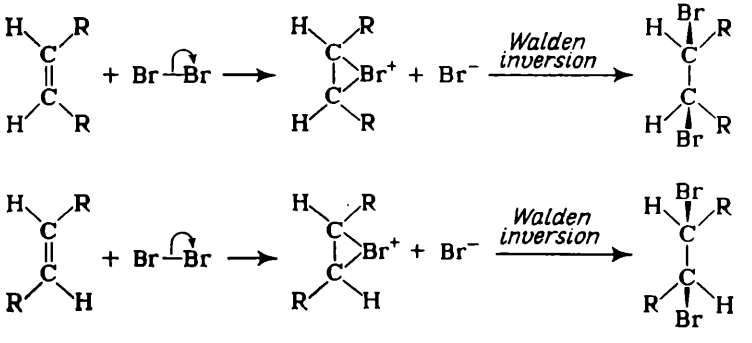
(that is, a *trans*-addition takes place) and the *trans*-olefin forms a *meso*-form:



As a rule, other electrophilic additions occur in the same way. An explanation for this *trans*-addition was given by Winstein who found out that the attacking electrophilic particle first (possibly through the stage of a π-complex) adds on to both unsaturated atoms,

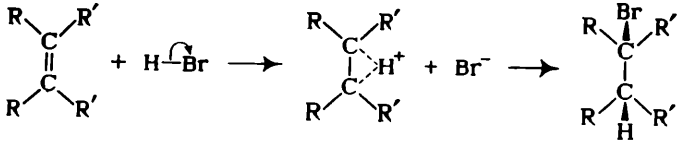
forming a three-membered onium ring (the bromonium ion in this case), which after the subsequent nucleophilic attack of the anion is opened with a Walden inversion. As a result, the first (electrophilic; Br^+ in the given example) and the second (nucleophilic; Br^- or CH_3O^- in this case) attacking particles are invariably found to have added on in the *trans*-position, so that a racemate is obtained.

From *trans*-olefins there is obtained a *meso*-form:

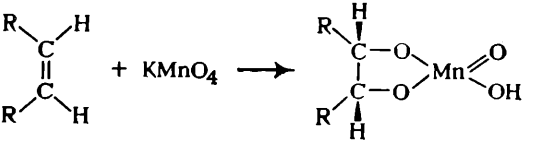


Stable bromonium and chloronium compounds are known to exist in the aromatic series (see Volume IV).

In the case of the addition of hydrogen halide, which also proceeds by the *trans*-type mechanism, a protonium compound with non-classical chemical bonds (two electrons per 3 atoms) is believed to exist transiently:

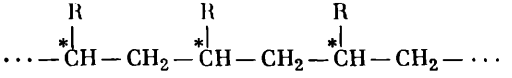


Addition reactions seldom take place in the *cis*-position. The Wagner oxidation of olefins by permanganate considered earlier (page 49) occurs as a *cis*-addition because the transiently formed cyclic acid ester $H_3\overset{V}{M}nO_4$ (see Volume I, page 339) is hydrolysed, the C—O bond remaining untouched and the Mn—O bonds being broken (without Walden inversion):



XIII. Stereoregular Polymers

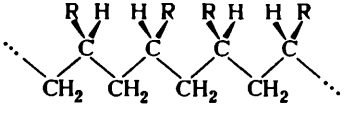
At this point it is convenient to consider stereoregular polymers. The free-radical (for example, peroxide-initiated) polymerization of the monomer $R-CH=CH_2$ results in the formation of a structure already familiar to us, which contains asymmetric atoms (marked by an asterisk):



These atoms are arranged with no definite sequence of their configurations being followed.

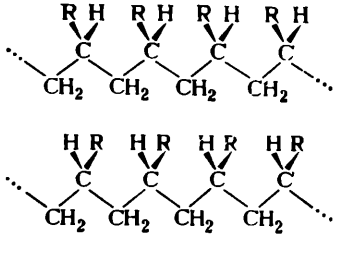
A different kind of polymerization, called **stereospecific polymerization,** was first discovered by C. E. Schildknecht in 1948 when he effected the polymerization of styrene under the action of boron trifluoride, and developed extensively by Natta, who introduced a heterolytic polymerization of the anionic type. Stereospecific polymerization results in the formation of **stereoregular polymers** of two types, with different stereochemical chain structures:

1. **Syndiotactic polymers**



in which the configurations of the asymmetric atoms alternate regularly and the chain as a whole is an inner racemate.

2. **Isotactic polymers**



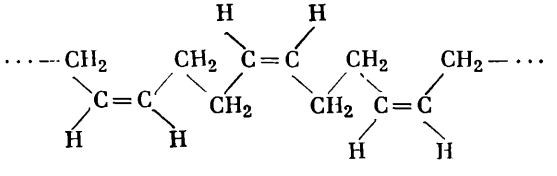
One chain contains only left-handed configurations; and the other is enantiomeric to it. This pair of chains is a racemate.

As compared with random **atactic polymers,** isotactic and syndiotactic polymers have a much higher mechanical strength and a much higher softening point owing to the regular crystalline packing of molecules. This may be illustrated by the following comparison:

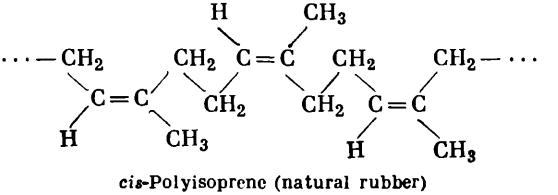
	Polypropylene	
	atactic	isotactic
Density, g/cm³	0.85	0.92
Melting point, °C	80	165-170

The tensile strength of isotactic polypropylene amounts to 350-410 kg/cm², i.e., corresponds to the strength of steel in order of magnitude, and is not lower than that of polyamide fibre.

In synthetic rubbers—the polymers of butadiene and isoprene polymers—the situation is as follows. The anionic polymerization effected by the action of lithiumalkyls (the anion is an alkyl) gives 1,4 polybutadiene or 1,4-polyisoprene, respectively. The stereoregularity of these polymers is of a different nature since they have no asymmetric carbon atoms. Their chains have the *cis*-configuration only:



cis-Polybutadiene



cis-Polyisoprene (natural rubber)

The *cis*- and *trans*-configurations are considered with respect to chain propagation.

Ziegler catalysts [$Al(C_2H_5)_3 + TiCl_4$], which were widely utilized in the investigations of Ziegler and Natta, also cause stereospecific polymerization. Heterogeneous catalysts have also been discovered, which function at an elevated temperature, the reactions leading to the formation of stereoregular polymers; an example is chromium oxide (and also vanadium and molybdenum oxides) on aluminium oxide.

Stereospecific polymerization is probably a heterolytic reaction.

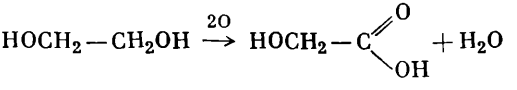
C. Synthesis of Hydroxy Acids

It is evident that the general and already considered methods of introducing carboxyl and hydroxyl groups into compounds are also used, in one or another degree, for synthesis of hydroxy acids.

But not all the methods are equally applicable to the synthesis of the various types of hydroxy acids, because α-, β-, γ-, etc., hydroxy acids differ rather strongly in properties and in methods of preparation.

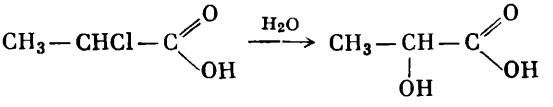
Synthesis of α-Hydroxy Acids. α-Hydroxy acids may be obtained by the following methods.

1. By the oxidation of the most available of glycols, 1,2-glycols, with a terminal primary alcoholic group:



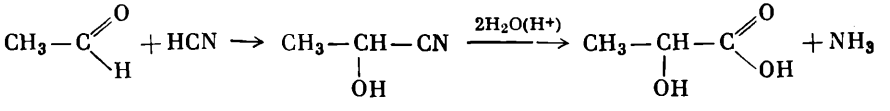
Glycolic acid

2. By the hydrolysis of α-halogen-substituted acids:

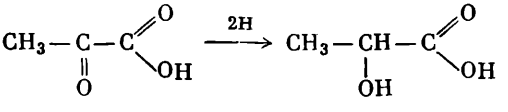


Lactic acid or
α-hydroxypropionic acid

3. By the cyanohydrin synthesis:



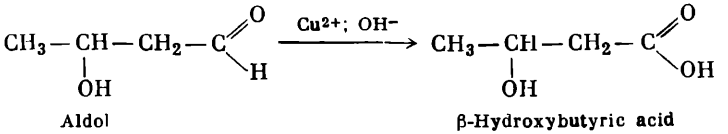
4. By the reduction of α-aldehydic or α-ketonic acids:



Pyruvic acid Lactic acid

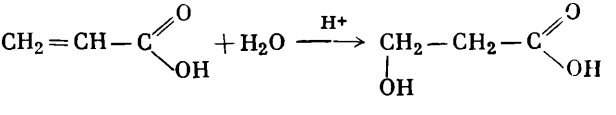
Synthesis of β-Hydroxy Acids. The methods used for preparing β-hydroxy acids are as follows.

1. The oxidation of aldols:

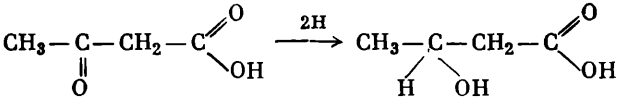


Aldol β-Hydroxybutyric acid

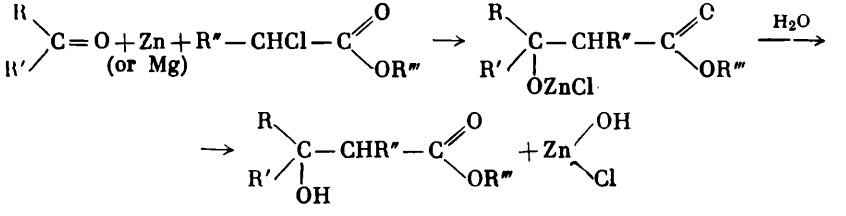
2. The addition of water to α-unsaturated acids:



3. The reduction of β-keto acids:



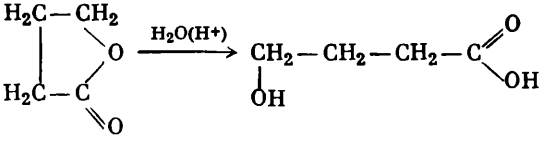
4. The Reformatsky reaction:



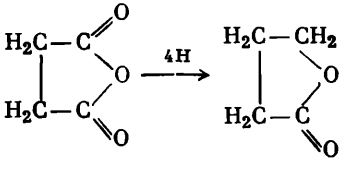
where R′ and R″ may also be hydrogen atoms.

The Reformatsky reaction finds extensive use in complicated syntheses.

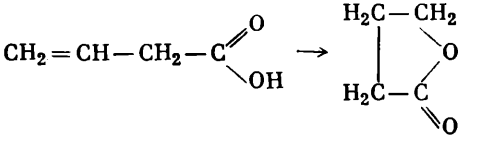
Synthesis of γ-Hydroxy Acids. The γ-hydroxy acids can be made by the hydrolysis of the corresponding internal esters—lactones:



which are prepared by the reduction of cyclic acid anhydrides:

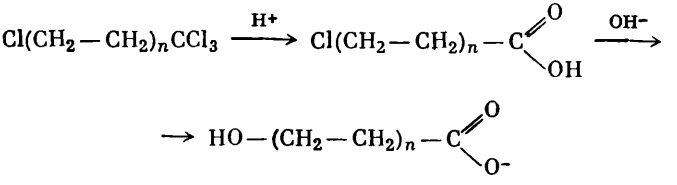


or by heating β-unsaturated acids with dilute mineral acids:



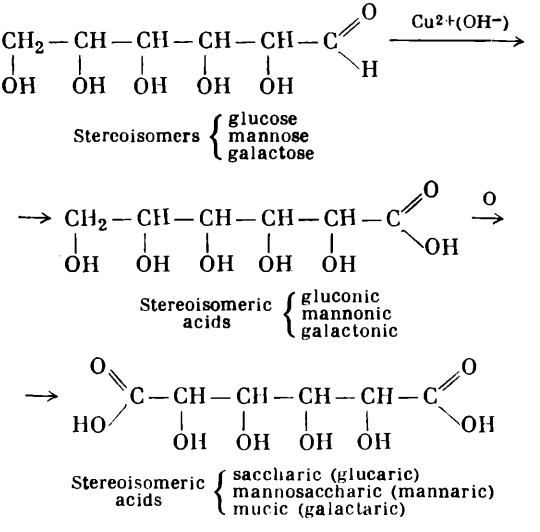
Synthesis of Acids with a Remote Terminal ω-Position of the Hydroxyl. Such acids can be produced by the successive acidic and then alkaline hydrolysis of tetrachloroalkanes—the products of telomerization (see Volume IV, "Free Radicals") of ethylene with

carbon tetrachloride (Freidlina):

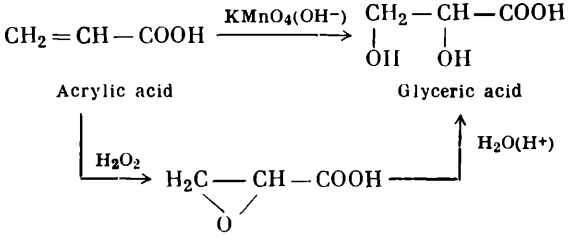


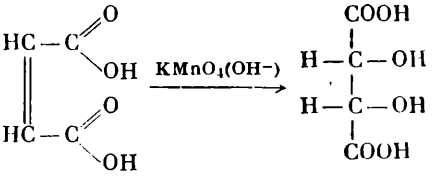
Besides, there exist specific methods of preparation of a number of important hydroxy acids, in particular polyhydroxy acids. Examples are given below.

1. The oxidation of monosaccharides (page 102):



2. The oxidation of unsaturated acids by the Wagner method ($KMnO_4 + OH^-$), by hydrogen peroxide or acid hydroperoxides (Prilezhaev). In the last two cases the reaction proceeds with subsequent opening of the epoxide ring under the influence of water in acid medium:





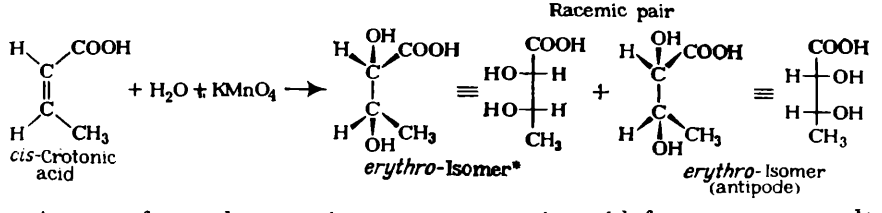
Maleic acid Mesotartaric acid

The stereochemistry of the course of reactions effected by the action of various oxidizing agents is best illustrated by the oxidation of *cis*- and *trans*-crotonic acids.

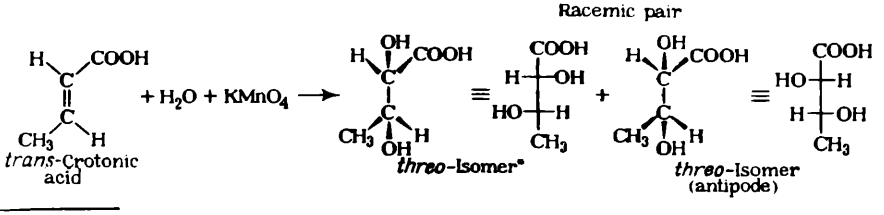
The Wagner oxidation by permanganate proceeds as a *cis*-addition (this is explained on page 53).

The *cis*-addition of oxygen to the *cis*-isomer of crotonic acid leads to both antipodes of the *erythro*-form of α,β-dihydroxybutyric acid.

Let us recall that the Wagner oxidation of maleic acid yields mesotartaric acid. These two cases differ from each other by the fact that the oxidation of maleic acid gives two structurally identical asymmetric carbon atoms having opposite configurations and the compound obtained is found to be optically inactive due to internal compensation. But in the case of *cis*-crotonic acid the asymmetric carbon atoms are different, as a result of which two antipodes are obtained—one antipode when hydroxyls add on from above the plane of the molecule of *cis*-crotonic acid, and the other when the addition takes place from below the plane:



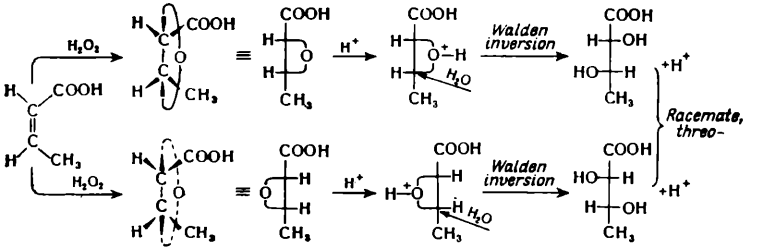
As seen from the reaction, *trans*-crotonic acid forms, as a result of the Wagner oxidation by permanganate, two antipodes of the *threo*-stereoisomer of α,β-dihydroxybutyric acid:



* The terms *threo* and *erythro* denote the diastereomers of compounds containing two neighbouring asymmetric carbon atoms. The *erythro*-isomer (the name is derived from the tetrose erythrose) resembles mesotartaric acid in configuration; the *threo*-isomer (from threose) resembles tartaric acids.

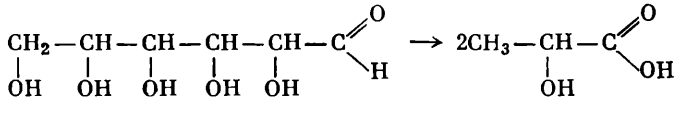
just as fumaric acid gives a racemate, racemic acid, as a result of the same reaction.

The Prilezhaev oxidation by means of acyl hydroperoxide or hydrogen peroxide proceeds via the formation of an epoxide. This is also a *cis*-addition of an oxygen atom across the double bond. The epoxide then undergoes protonation at the bridge oxygen atom and the oxonium compound is attacked by water, which opens the ring with a Walden inversion at the carbon atom being attacked. It is the β-carbon atom which is attacked since in α,β-unsaturated acids the orientation of the attack is determined by the carboxyl group, which causes an anti-Markovnikov addition, and in the case of α,β-epoxy acids (glycidic acids) an anti-Kraus opening of the ring takes place:



Thus, the oxidation by hydrogen peroxide leads to a different diastereomer than the permanganate oxidation.

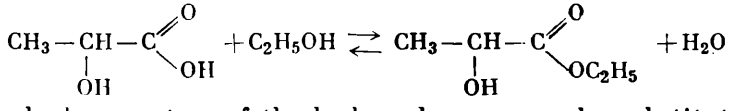
3. Preparation of lactic acid by fermentation of sugars (glucose, milk sugar—lactose, saccharose) by the action of lactic fermentation bacteria (*Bacillus acidi laevalactici*, etc.). Depending on the bacterial species, there may be formed levorotatory or racemic acid. The overall equation is as follows:



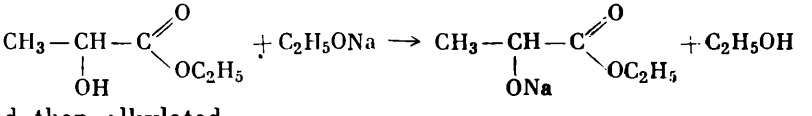
Technically, racemic lactic acid is produced by the fermentation of saccharose or maltose by means of the bacteria *Bacillus Delbrücki* at 50°C, the required nutritious substances (PO_4^{3-}, NH_4^+) being added and the neutralization effected gradually with chalk.

D. Properties and Reactions of Hydroxy Acids

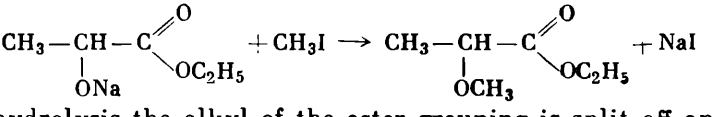
Hydroxy acids are stronger than their parent carboxylic acids. This is particularly true of α-hydroxy acids. The increased acidity is due to the *—I* effect of the hydroxyl group in the saturated chain of carbon atoms. Like ordinary carboxylic acids, hydroxy acids are capable of forming esters with alcohols:



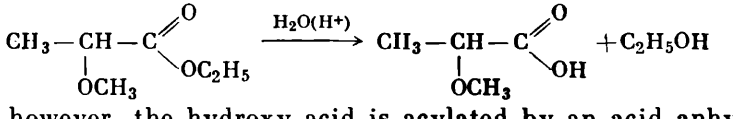
The hydrogen atom of the hydroxyl group can be substituted by sodium through the action of sodium alkoxide (or metallic sodium)



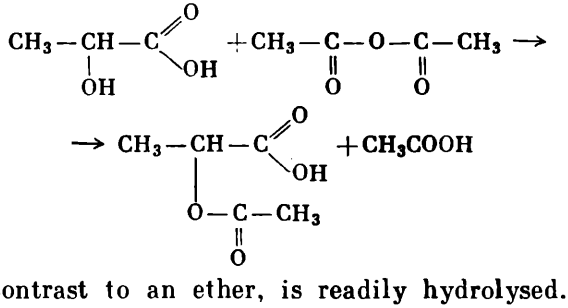
and then alkylated



On hydrolysis the alkyl of the ester grouping is split off and the ether of the hydroxy acid is left:



If, however, the hydroxy acid is acylated by an acid anhydride or acid chloride, the alcoholic function enters into the esterification reaction and an ester is formed:



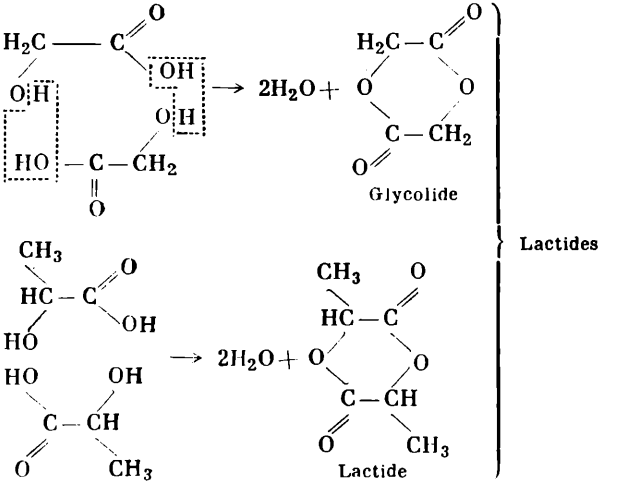
which, in contrast to an ether, is readily hydrolysed.

Hydroxy acids also give other functional derivatives which are characteristic of acids and alcohols.

The oxidation at the hydroxyl group converts hydroxy acids into aldehydic and ketonic acids.

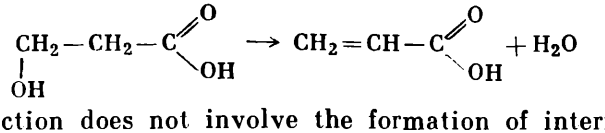
The most specific reaction of hydroxy acids is the formation of internal cyclic esters, i.e., the esterification of their own hydroxyl by their own carboxyl. In this case, there becomes prominent the preferable formation of five- and six-membered rings common to all organic chemistry as a whole.

α-Hydroxy acids also form internal six-membered heterocyclic esters (from two molecules) which are collectively called **lactides:**

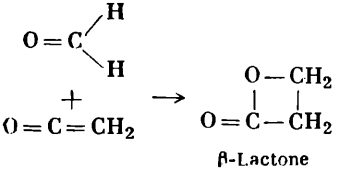


In acid medium, lactides are hydrolysed to the parent α-hydroxy acids.

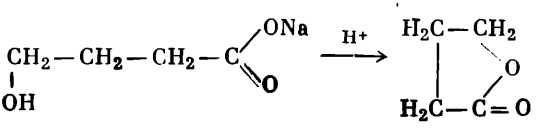
β-Hydroxy acids when heated by themselves readily eliminate water and are transformed into α,β-unsaturated acids:



This reaction does not involve the formation of internal esters (because of the low stability of the four-membered ring). Certain β-lactones can however be obtained in a different way, say, from formaldehyde and ketene:

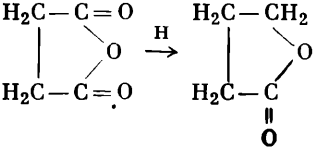


γ-Hydroxy acids readily undergo spontaneous cyclization into γ-lactones, for example, when their salts are acidified:



γ-Butyrolactone

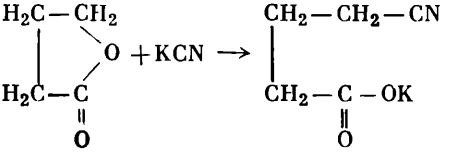
γ-Lactones constitute an important class of compounds. These compounds have been discovered by Zaitsev who prepared butyrolactone by the reduction of succinic anhydride:



According to the Geneva nomenclature, γ-lactones are named by replacing the final *-e* in the names of the corresponding alkanes by the ending *-olide*; for example, butanolide.

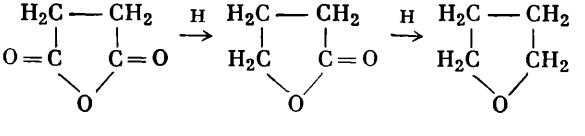
Alkalis hydrolyse γ-lactones, converting them into salts of the acids. Hydrogen halides convert them into γ-halogen-substituted acids by opening their rings.

Potassium cyanide open the rings of lactones according to the following scheme:

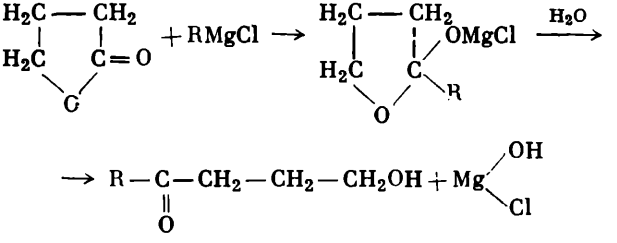


This reaction is a rather important procedure in the synthesis of dicarboxylic acids.

The reduction of butyrolactone leads to tetrahydrofuran. The reduction of succinic anhydride to tetrahydrofuran provides a conclusive proof of the structure of butyrolactone:

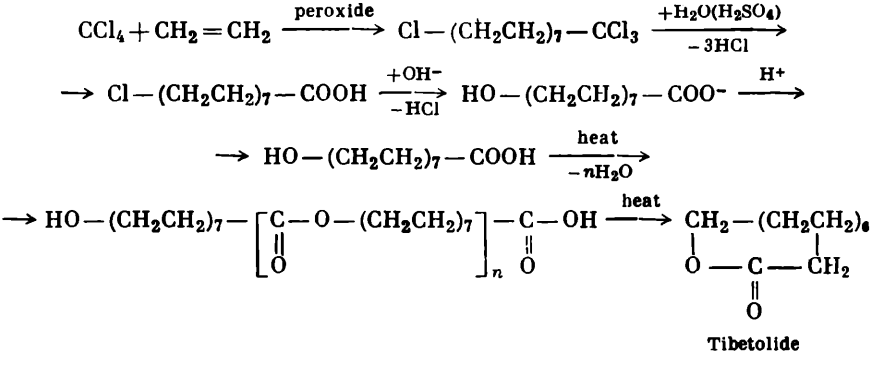


With Grignard reagents the lactones react to form hydroxy ketones:



ω-Lactones with nine and ten carbon atoms (nonanolide and decanolide) are found in small amounts in milk and milk products and are partially responsible for the odour of butter (together with $CH_3-\overset{\overset{O}{\|}}{C}-\overset{\overset{O}{\|}}{C}-CH_3$, $CH_3-\underset{\underset{OH}{|}}{CH}-\overset{\overset{O}{\|}}{C}-CH_3$ and other substances). It is for this reason that they are used to impart a flavour to margarine.

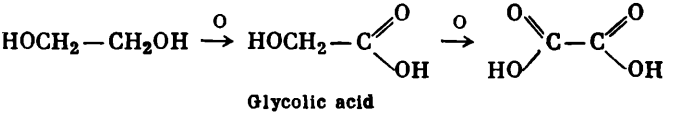
Lactones with even larger rings are known, though ω-hydroxy acids do not undergo cyclization into such lactones spontaneously. For example, the lactone known as **tibetolide**, which is widely utilized as flavouring matter with the odour of musk and as a stabilizing agent for perfumes, is obtained in the following way (Freidlina and Belov)



Tibetolide

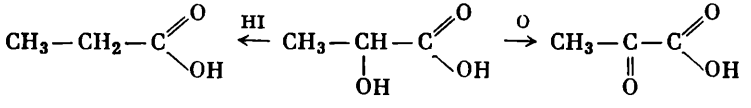
E. Proof of the Structure of Some Hydroxy Acids

The structure of **glycolic acid** becomes clear from its relation to ethylene glycol and oxalic acid:



Glycolic acid

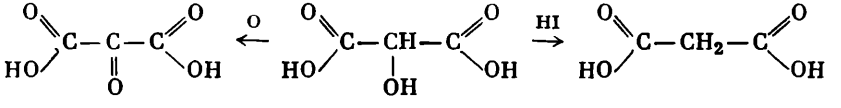
Lactic acid (*racemic α-hydroxypropionic acid*) is reduced by hydrogen iodide to propionic acid, which establishes its skeleton, and is oxidized to a keto acid—pyroracemic, or pyruvic, acid, from which it follows that it contains a secondary alcoholic group:



Lactic acid

The syntheses described on page 56 provide a conclusive proof of the structure of lactic acid as an α-hydroxypropionic acid.

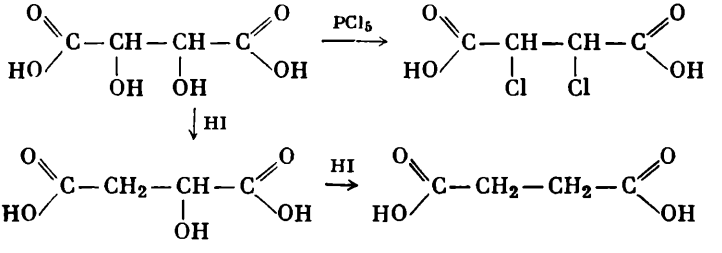
Tartronic acid is oxidized to a keto acid—mesoxalic acid—and is reduced to malonic acid:



Mesoxalic acid | Tartronic acid | Malonic acid

Tartronic acid is prepared by the hydrolysis of chloromalonic acid.

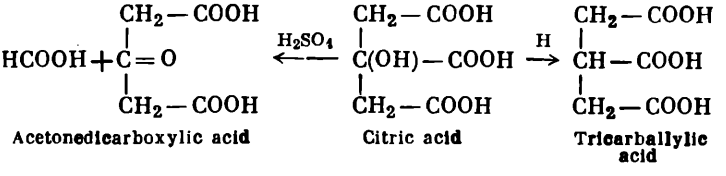
The structure of **tartaric acids** is established by their conversion into dichlorosuccinic acid through the replacement of hydroxyls by chlorine (PCl_5) and the reduction by HI first to malic and then to succinic acid:

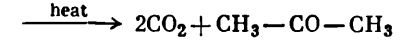


Malic acid | Succinic acid

Citric acid has three carboxyl groups (titration with alkali) and one tertiary hydroxyl group (stability to oxidation). The reduction of citric acid leads to the formation of tricarballylic acid, and when it is heated with sulphuric acid, formic and acetonedicarboxylic acids result; the latter when heated decomposes into carbon dioxide

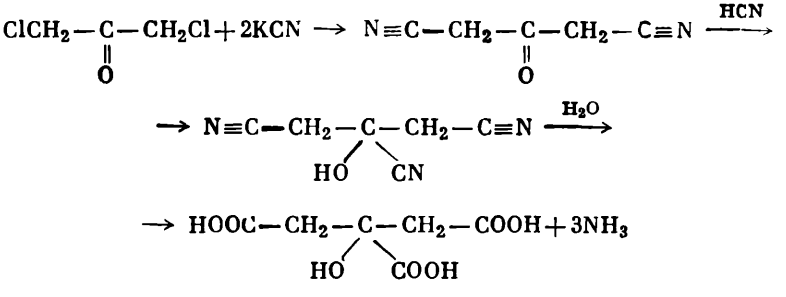
and acetone:





The formation of a carbonyl group with elimination of HCOOH is typical of α-hydroxy acids. This means that the central carbon atom, which has become a carbonyl carbon atom, originally carried both a carboxyl and a hydroxyl.

The structure of citric acid has been proved by its synthesis:



F. Importance of Hydroxy Acids

Hydroxy acids occur widely in the vegetable world. Glycolic acid, $HOCH_2—COOH$, is found in many plants (beet, grape). Lactic acid, $CH_3CH(OH)COOH$, as has already been mentioned, is the product of the life activity of a number of bacteria. It has long been used as a preservative agent. Sour milk, curdled milk (clabber), kefir, varenets are the products of the lactic fermentation of milk: milk sugar—lactose—is converted to lactic acid which coagulates the protein (the caseine of milk). The preparation of sour cabbages, wetted apples, and the pickling of cucumbers, tomatoes, water melons, etc.—all these processes are based on the lactic fermentation of sugars contained in these vegetables and fruits. The accumulated lactic acid serves for preserving vegetables. Silage is the product of the lactic fermentation of the stalks and leaves of root-bearing plants (haulm) and greens.

All that has just been said refers to L- and D-lactic acids. The muscles contain D-lactic (sarcolactic) acid, which is formed from glucose in a similar way and is accumulated during the functioning of muscles. Its precursor is the simplest keto acid—pyroracemic acid which is reduced to lactic acid.

The formation of pyroracemic (pyruvic) acid from glucose in biological processes is considered on page 132 et seq.

Malic acid is widely distributed in the vegetable kingdom, occurring for example in sour apples, grapes and the berries of the mountain ash. D-Tartaric acid is found in many fruits too in the free state and in the form of salts. It is precipitated as a difficultly soluble acid salt of potassium in vats containing fermenting wine, and it is from this cream of tartar (potassium bitartrate) that tartaric acid, i.e., D-tartaric acid*, is produced. Citric acid, $HOOCCH_2C(OH)(COOH)CH_2COOH$, occurs in the free state in lemons, oranges, currants and other fruit, from which it is prepared. In this country, citric acid is produced from tobacco (*Nicotiana rustica*) after the removal of nicotin, and also from the leaves of Asiatic cotton (A. S. Sadykov). It is also prepared by citric fermentation of sugars (glucose, maltose, molasses) with the aid of citromyces.

All these α-hydroxy acids are harmless to man and many of them (lactic, tartaric, citric) are used in cookery and for preparing beverages.

Citric and malic acids play an important part in many biochemical processes taking place in all cells, in particular, in cellular respiration (see the Krebs cycle, page 135).

4.3. Aldehydic and Ketonic Acids

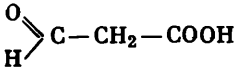
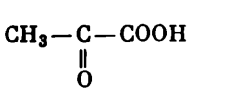
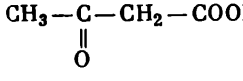
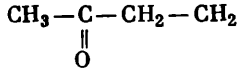
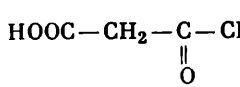
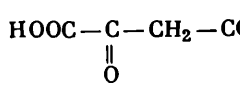
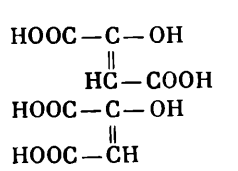
In their properties, α-, β- and γ-carbonyl acids (ketonic or aldehydic acids) differ sufficiently sharply from one another. Also, aldehydic acids differ from ketonic acids in just the same way as aldehydes differ from ketones.

Table 4.5 presents the names and physical properties of a number of aldehydic and ketonic acids.

Since the keto (or carbonyl) group is a strong electron-attracting group, which exhibits sharply pronounced $-I$ and $-T$ effects, aldehydic and ketonic acids are stronger acids than the parent carboxylic acids, and α-keto acids are classified as belonging to the most powerful carboxylic acids.

* Sodium tartrate plus alkali dissolves copper hydroxide, giving a dark-blue Fehling's solution which is used for mild oxidation (for example, of aldehydes). The cupric ion in this reagent is linked to the four oxygen atoms of the hydroxyls of two molecules of the tartrate.

TABLE 4.5. **Aldehydic and Ketonic**

Formula	Acid	m.p., °C
	Glyoxalic	98 (anh.)
	Formylacetic	Has not
	Pyruvic or pyroracemic	13.6
	Acetoacetic*	—
	Levulinic (levulic)	37.2
	Acetonedicarboxylic	135 (dec.)
	Oxalacetic	—
	Tautomeric forms	184 152

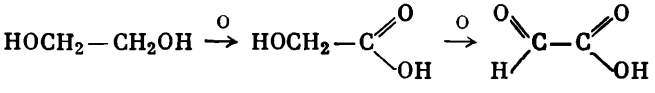
* A colourless viscous non-crystallizable liquid.

Acids and Their Esters

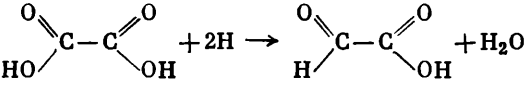
b.p., °C	K_a (at 25°C)	Ester	m.p., °C	b.p., °C
—	5×10^{-4}	—	—	—
been isolated in the free state		Not isolated		
165 (dec.)	3.2×10^{-3}	Methyl Ethyl	— —	137 144.55 (at 17 mm Hg)
< 100 (dec.)	2.62×10^{-4} (at 18°C)	Methyl Ethyl	Below —80 —	170 180
246; 154 (at 14 mm Hg)	2.4×10^{-5}	Ethyl Methyl	— —	205.8 196
Dec.	7.9×10^{-4}	—	—	—
—	—	Diethyl Dimethyl	— 74	132 (at 24 mm Hg)
—	—	—	—	—
—	—	—	—	—

A. Synthesis of Aldehydic and Ketonic Acids

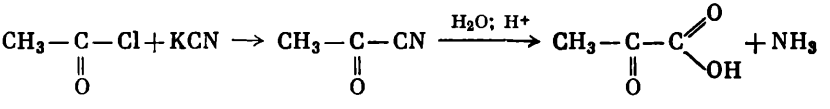
The synthesis of aldehydic and ketonic acids can be accomplished by using many of the ordinary methods of introducing a carboxyl and a carbonyl group. Such are, for example, the synthesis from chlorosubstituted carbonyl compounds via nitriles; the oxidation of the primary alcoholic group of ketoalcohols to the carboxyl; the oxidation of the primary or secondary alcoholic group of hydroxy acids to the carbonyl (keto) group; the hydrolysis of *gem*-dihalo-substituted* carboxylic acids to aldehydic and ketonic acids; the reduction (for example, electrochemical) of one of the two carboxyl groups of dicarboxylic acids to the aldehyde group. For instance, the simplest of the aldehydic acid, **glyoxalic acid**, is prepared by the oxidation of glycolic acid and also of ethylene glycol, say, with nitric acid:



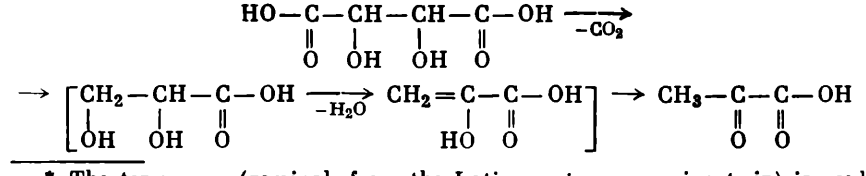
and by the electrolytic cathodic reduction of oxalic acid on the cathode:



The simplest α-ketonic acid, **pyruvic acid**, like other α-ketonic acids, can be made via a nitrile:



α-Ketonic acids are also conveniently prepared by the oxidation of α-hydroxy acids. Some of the methods, say, the incorporation of a carboxyl group by means of organomagnesium compounds, are of course inapplicable here. There are, however, important specific methods of synthesis of aldehydic and ketonic acids, which call for our consideration. For instance, the pyrolysis of tartaric acid (which is a special case) gives pyruvic acid:



* The term *gem*- (geminal, from the Latin *geminus*, meaning twin) is used to show the positions of two identical substituents attached to the same carbon atom.

(The formulas in square brackets disclose the meaning of the reaction but do not represent any of the isolated intermediate products and the stages of the process.)

A specific method of synthesis of β-ketonic acids is the reaction of ester condensation—the Geuther-Claisen condensation. This reaction consists in that an ester of a carboxylic acid or a mixture of two esters of two different carboxylic acids is allowed to interact with metallic sodium (or with a sodium alkoxide). The formal summary equations are as follows:

$$\begin{aligned} &H-\overset{\overset{O}{\|}}{C}-OC_2H_5 + CH_3-\overset{\overset{O}{\|}}{C}-OC_2H_5 \xrightarrow{Na} \\ &\rightarrow H-\overset{\overset{O}{\|}}{C}-CH_2-\overset{\overset{O}{\|}}{C}-OC_2H_5 + C_2H_5ONa + {}^1/_2H_2 \end{aligned} \quad (1)$$

$$\begin{aligned} &CH_3-\overset{\overset{O}{\|}}{C}-OC_2H_5 + CH_3-\overset{\overset{O}{\|}}{C}-OC_2H_5 \xrightarrow{Na} \\ &\rightarrow CH_3-\overset{\overset{O}{\|}}{C}-CH_2-\overset{\overset{O}{\|}}{C}-OC_2H_5 + C_2H_5ONa + {}^1/_2H_2 \end{aligned} \quad (2)$$

These equations, however, do not reveal the meaning of the process and are inaccurate in the sense that sodium ethoxide is not indifferent with respect to the esters of β-ketonic acids (it is more convenient to discuss these relations after the consideration of the keto-enol tautomerism).

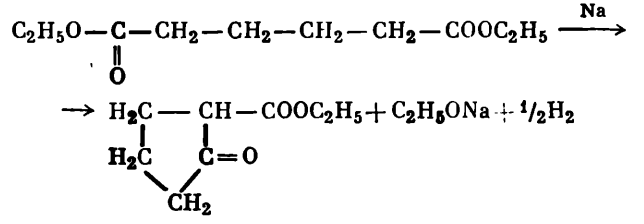
Ester condensation can also be carried out between dicarboxylic and monocarboxylic esters and between the esters of two different dicarboxylic acids:

$$\begin{aligned} &C_2H_5O-\overset{\overset{O}{\|}}{C}-\overset{\overset{O}{\|}}{C}-OC_2H_5 + CH_3-\overset{\overset{O}{\|}}{C}-OC_2H_5 \xrightarrow{Na} \\ &\rightarrow C_2H_5O-\overset{\overset{O}{\|}}{C}-\overset{\overset{O}{\|}}{C}-CH_2-\overset{\overset{O}{\|}}{C}-OC_2H_5 + C_2H_5ONa + {}^1/_2H_2 \end{aligned} \quad (3)$$

In the last case, cyclic ketonic acids are formed (the Dieckmann reaction):

$$\begin{array}{l} O=C-OC_2H_5 \\ \quad | \\ O=C-OC_2H_5 \end{array} + \begin{array}{l} COOC_2H_5 \\ | \\ CH_2 \\ \diagdown \\ \quad CH_2 \\ \diagup \\ CH_2 \\ | \\ COOC_2H_5 \end{array} \xrightarrow{2Na} \begin{array}{l} \quad\quad COOC_2H_5 \\ \quad\quad\quad | \\ O=C-CH \\ \quad\quad\quad\diagdown \\ \quad\quad\quad\quad CH_2 \\ \quad\quad\quad\diagup \\ O=C-CH \\ \quad\quad\quad | \\ \quad\quad COOC_2H_5 \end{array} + 2C_2H_5ONa + H_2 \quad (4)$$

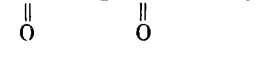
Dicarboxylic esters with a longer hydrocarbon chain are capable of condensing with themselves (self-condensation):



As is always the case, cyclization reactions readily give only five- and six-membered ring compounds.

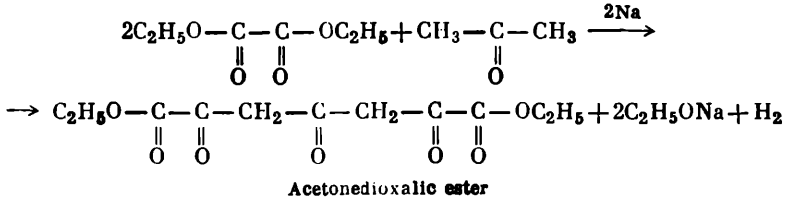
From all these examples it is clear that the condensation is associated with the presence, in an ester which is the second component in the reaction, of a free alpha-hydrogen atom (or, even better, an unsubstituted methylene linkage, i.e., two alpha-hydrogen atoms). The reaction is essentially the acylation of one ester by another at the alpha-carbon atom. The esters formed are therefore called **formylethylacetic ester** or **ethyl formylacetate** (reaction 1); **ethyl acetylacetate** or **acetoacetic ester** (reaction 2); and **oxalacetic (oxysuccinic) ester** (reaction 3). Of course, the esters thus obtained can be converted by hydrolysis into the corresponding free aldehydic and ketonic acids.

From the esters of β-ketonic acids we can easily prepare the esters of the homologous ketonic acids since under the action of a metal or alkoxide the hydrogen atoms of the α-linkage



are readily ionized and replaced by sodium (page 89), and such a sodium derivative can be alkylated by an alkyl halide (examples are given on page 97).

The esters can also be condensed with ketones. This results in the formation of β-diketones. If, however, oxalic ester is condensed with ketones, the esters of β-ketonic acids will be formed, which are simultaneously the esters of α-ketonic acids; for example,



Acetonedioxalic ester

Thus, the ester condensation method appears to be one of the most powerful synthetic methods for building the skeletons of organic molecules.

γ-Ketonic acids, the simplest representative of which is **levulinic acid**

$$CH_3-\overset{\overset{O}{\|}}{C}-CH_2-CH_2-\overset{\overset{O}{\|}}{C}-OH$$

can be made via the sodium derivatives of the esters of ketonic acids (in this particular case, via the sodium derivative of acetoacetic ester). Levulinic (levulic) acid is also obtained by boiling levulose (fructose) and other hexoses (hence its name) with concentrated hydrochloric acid.

In connection with the fact that keto-enol tautomerism plays an enormous part in the chemistry of aldehydic and ketonic acids, especially β-ketonic acids and their functional derivatives, it is necessary at this point to direct our attention to the problems of tautomerism.

XIV. Tautomerism

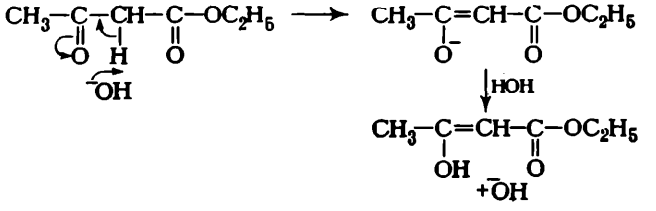
All the esters of β-keto acids, which have the C—H or CH_2 group in the alpha-position, are clearly defined tautomeric compounds. Let us consider, as an example, the tautomerism of acetoacetic ester (ethyl acetoacetate). It can easily be shown that acetoacetic ester is not an individual compound but rather a mixture of two reversibly interconvertible isomers:

$$\underset{\text{I}}{CH_3-\overset{\overset{O}{\|}}{C}-CH_2-\overset{\overset{O}{\|}}{C}-OC_2H_5} \rightleftarrows \underset{\text{II}}{CH_3-\overset{\overset{OH}{|}}{C}=CH-\overset{\overset{O}{\|}}{C}-OC_2H_5}$$

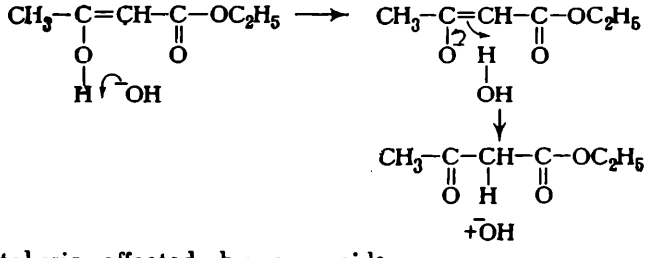
As a result, the equilibrium of two **tautomeric forms** or **tautomers**, I and II, is established (I is the keto form and II is the enol form). The relationship between or interconversion of the ketonic and enolic forms is referred to as **tautomerism** or **tautomerization.** The position of equilibrium depends on temperature and, to a strong extent, on the solvent used. The rate of interconversion of the tautomers is different under different conditions. It increases considerably when the reaction is catalysed by hydrogen or hydroxyl ions and, in general, by bases, even by glass.

The acid-base catalysis of this tautomerization reaction is one of the numerous examples of acceleration of reactions through the action of hydrogen and hydroxyl ions. The factors responsible for this phenomenon can be ascertained from the following schemes.

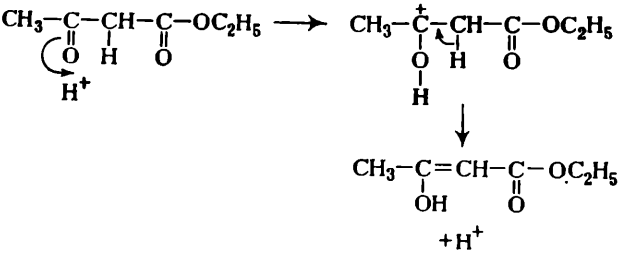
(1) Catalysis effected by a base:



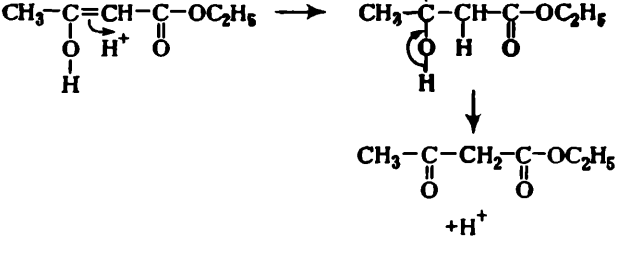
(2) Reverse conversion:



(3) Catalysis effected by an acid:



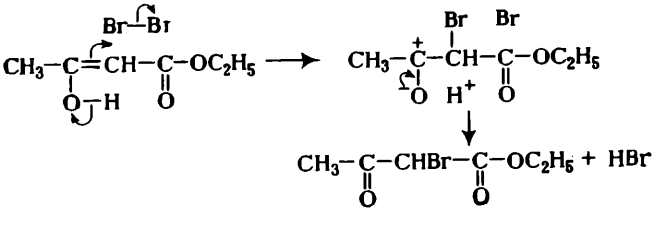
(4) Reverse conversion:



Therefore, on distillation in the absence of glass, say, from a quartz flask, the first fraction distilled off is the lower-boiling enol

form. The rate of the interconversion of the two isomers (tautomerization) at the temperature at which vacuum distillation is carried out is not high and the separation of the two forms is successful to a certain extent. The distilled-off enol form when allowed to stand changes to the equilibrium mixture of the two forms. When the solution of acetoacetic ester in petroleum ether (a mixture of the hydrocarbons C_nH_{2n+2}) is cooled with liquid air, a pure keto form (m.p. —39°C) crystallizes out. At room temperature it also returns slowly to the equilibrium mixture. Under the conditions of chemical reactions acetoacetic ester, i.e., a mixture of the keto and enol forms, normally reacts in one of the possible directions only (either as a ketone or as an enol), as if it were an individual compound. As one of the forms is removed from the reaction system upon completion of the reaction, the other form is again partly converted to the first according to the equilibrium laws and the reaction is continued.

One of the few reactions that can be used to trace out and determine quantitatively the percentage content of one of the forms in the mixture, namely the enol form, is the reaction of addition of bromine across the double bond:

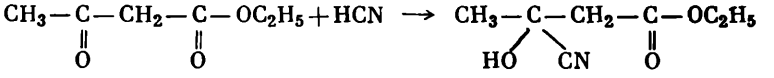


If the reaction is conducted in the cold and made to proceed sufficiently rapidly, the entire enol form can be titrated (K. Meyer) before it is noticeably converted to the keto form. In this way, the enol content has been determined in a number of tautomeric substances in various solvents. These figures are presented in the table of ionization constants (see page 83).

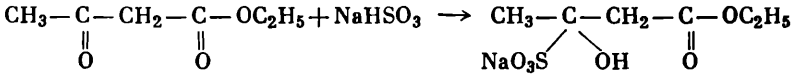
The percentage content of the keto and enol forms in an equilibrium mixture can be deduced from the physical properties of the mixture since the keto and enol forms show different light absorption in the ultraviolet region and have different refractive indices. On the basis of such data Knorr calculated the contents of the two forms in the equilibrium mixture.

The majority of other reactions proceed identically both with the equilibrium acetoacetic ester and with the enol and the keto form separately. Let us consider some reactions of acetoacetic ester, which are characteristic of the structure of the two forms.

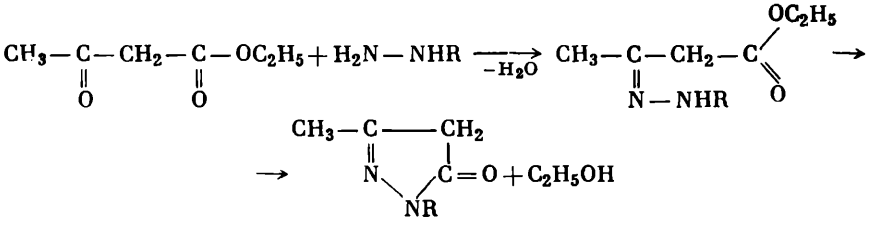
Reactions Proceeding According to the Keto Type. 1. Addition of hydrocyanic acid:



2. Addition of sodium bisulphite:

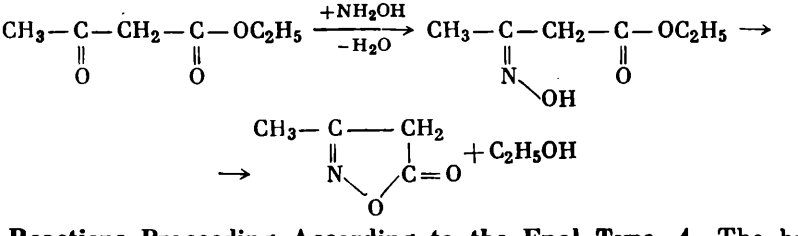


3. The reaction with substituted hydrazines:



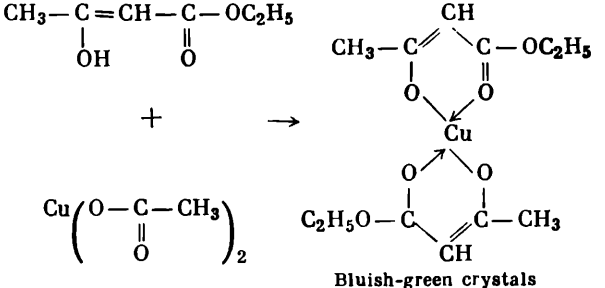
Here the ordinary reaction of the ketone is complicated by the second stage—the cyclization into R-methylpyrazolone (see Volume III).

4. The reaction with hydroxylamine proceeds in a similar way, involving the cyclization of the initially formed oxime:

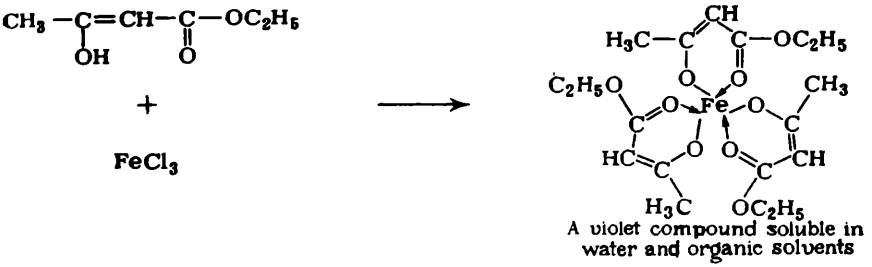


Reactions Proceeding According to the Enol Type. 1. The bromination across the double bond mentioned above.

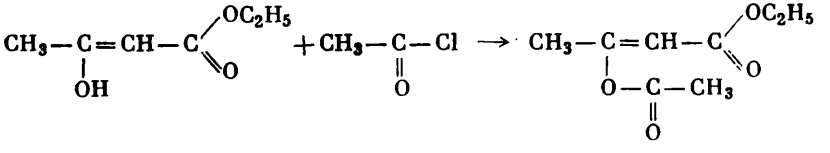
2. The formation of inner-complex enolates with metal salts. For example,



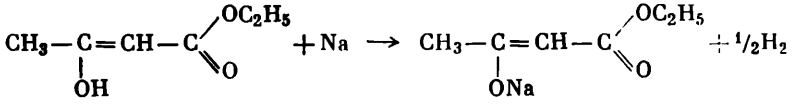
Bluish-green crystals slightly soluble in water



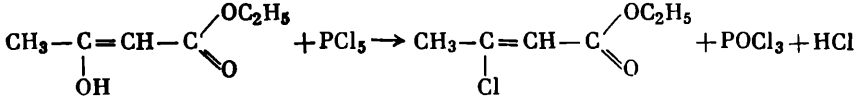
3. Acylation by acid chlorides in a pyridine solution:



4. The action of metallic sodium:

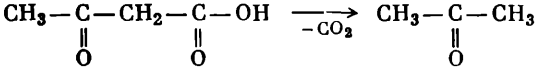


5. The action of phosphorus pentachloride (PCl_5):

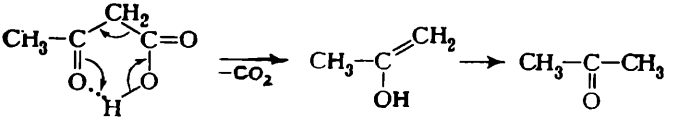


Besides, it is necessary to cite the reactions of acetoacetic ester which are not so closely related to its tautomerism and which are typical of all the esters of β-ketonic acids.

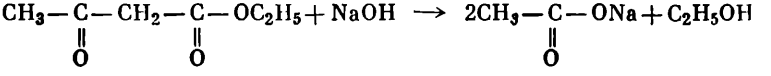
1. On hydrolysis in acid medium acetoacetic ester is converted into acetoacetic acid which when heated in an aqueous solution decarboxylates to acetone:



This is the so-called **ketonic cleavage** (or *splitting*) of β-keto acids. There is ground for believing that this ketonic splitting proceeds via the cyclic transition state and the enol form of the ketone:



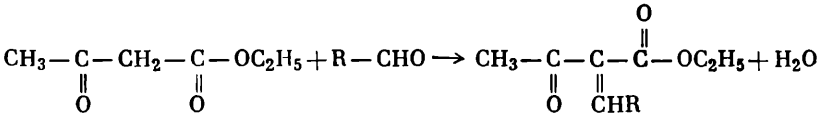
2. Under the influence of strong bases the cleavage of acetoacetic ester (in addition to the hydrolysis of the ester grouping) occurs across the bond between the carbonyl group and the central methylene group, and two molecules of acetic acid are formed (in the form of a salt):



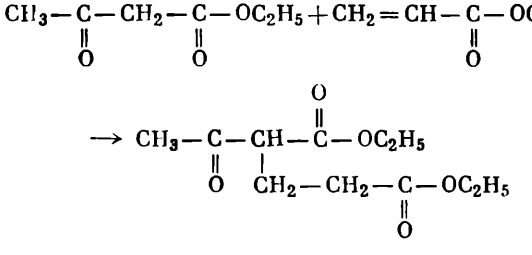
This is the carboxylic acid cleavage of acetoacetic ester.

A number of reactions, some of which will be given below, characterize the great mobility of the hydrogen atoms of the methylene group:

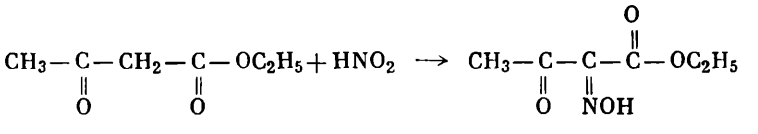
(a) the reaction with aldehydes:



(b) the Michael reaction (Volume I, pages 401, 411):



(c) the reaction with nitrous acid (*cf.* the reaction of ketones. Volume I, page 185):

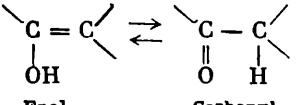


Reactions that occur according to the keto or enol type give a clear-cut picture of the dual reactivity of acetoacetic ester, which is most simply explained by the reversible isomerization, i.e., by the phenomenon of tautomerism. This was established (though in cases other than the above ones) even before the above-described conclusive experiments on the separation and quantitative determination of tautomers and on their interconversion.

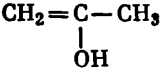
It is interesting to note that A. M. Butlerov predicted as far back as 1877, on the basis of the structure theory, the possibility of this dual reactivity and of tautomerism as a reversible isome-

rization. But the first phenomena of this kind were discovered by Baeyer in the eighties of last century not in the area of the keto-enol tautomerism discussed above for acetoacetic ester but for the so-called lactam-lactim tautomerism (page 86) of isatin; the pioneering investigations of keto-enol tautomerism date back to the very end of the 19th century and the beginning of the 20th century.

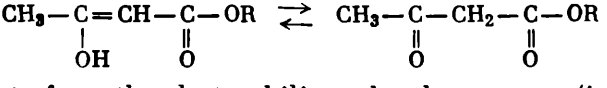
Keto-enol tautomerism is characterized by a reversible transformation:



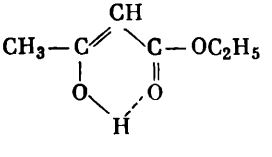
The Erlenmeyer-Eltekov rule (see Volume I, page 390) states that the enolic systems (the simplest ones) are unstable and are capable of isomerization into carbonyl compounds. Indeed, for monoketones and monoaldehydes the equilibrium is practically completely shifted to the right and the concentration of the enol form



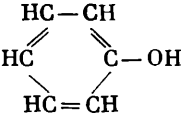
in acetone is only 2.5×10^{-4} per cent. This corresponds to the higher energy content of the enol form and to its higher acidity. To compensate for this difference, the appropriate structural changes must be introduced into the keto-enol system, which would make the enol form more favourable energetically. The nature of such ordinary structural changes can be seen from the example of acetoacetic ester:



In the keto form the electrophilic carboethoxy group (in addition to the carbonyl group) draws the electrons away from the methylene group and renders its hydrogen atoms more mobile (in other words, increases the acidity of the CH_2 group). The ethylenic double bond that has been formed in the enol form is found to be conjugated with the carbonyl double bond of the carboethoxy group. The conjugation gives an energy gain, i.e., decreases the energy of the system. Finally, the enol form is additionally stabilized by intramolecular hydrogen bonding—again a small additional energy gain:



As a result, the content of the enol form in acetoacetic ester is considerably higher than in acetone; it amounts to 7 per cent, but the enol form still remains somewhat less stable than the keto form. The enol-to-keto ratio is of course different for different substances (other conditions being equal). There are tautomeric systems in which the enol form predominates and is even the principal component, for example, in phenol:



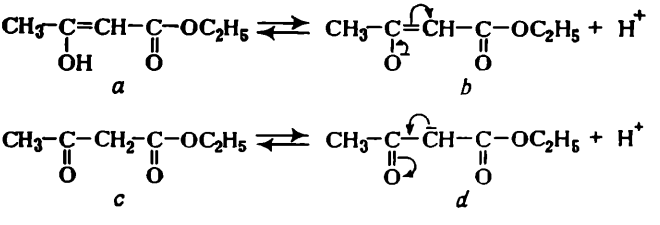
This ratio strongly depends on the solvent used.

The enol-to-keto ratio is conveniently expressed in terms of the equilibrium constant, where C_{enol} and C_{keto} are the corresponding concentrations, and K is the equilibrium constant which defines the ratio of these concentrations (**the enolization constant**). Below are given the values of $K = C_{enol}/C_{keto}$ for acetoacetic ester in various solvents at room temperature (20°C):

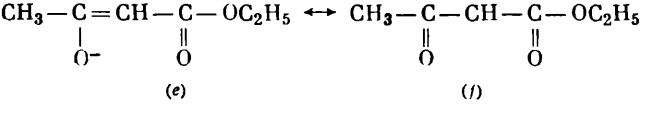
Water	0.004	Ethanol	0.13
Formic acid	0.011	Benzene	0.22
Methanol	0.074	Ether	0.43
		Hexane	1

The keto and enol undergo electrolytical dissociation differently in different solvents and this is why the enolization constants are different in different media.

The anion of the enol and keto forms has the same (resonance-stabilized, mesomeric) structure:



The formulas (*b*) and (*d*) express, in the language of mesomerism, the same structure; in terms of the resonance symbolism, this structure is expressed as follows:



This means that the actual structure is the one intermediate between the resonating structures (*e*) and (*f*), which does not of course imply that the intermediate structure lies exactly in the middle and the electron charge is distributed equally between oxygen and carbon. The charge is concentrated to a much higher extent on the electronegative oxygen and the actual structure of the anion is thus much closer to (*e*) than to (*f*).

Proceeding from the undoubtedly correct assumption of the identity of the enolic anion and ketonic anion, M. I. Kabachnik developed the fundamental theory of tautomerism in which the phenomenon is regarded as an acid-base equilibrium. His interpretation is presented here in a somewhat simplified form. When the enol and keto forms are electrolytically dissociated in solvents, such as water, alcohol, ether, benzene, these solvents do not remain indifferent and play the role of Lewis bases* (see Volume I, page 201). Therefore the equations for the electrolytic dissociation of the two tautomeric forms should be formulated as follows:

$$A_IH + S \rightleftarrows A^- + \overset{+}{S}H \quad (1)$$

$$A_{II}H + S \rightleftarrows A^- + \overset{+}{S}H \quad (2)$$

Here, for the sake of brevity, the following designations are introduced: A^- is the anion common to the keto and enol forms; A_IH is the keto form; $A_{II}H$ is the enol form; S is the solvent molecule which draws the proton and is converted into $\overset{+}{S}H$, a Lewis conjugate acid [$H_3\overset{+}{O}$ for water; $(C_2H_5)_2\overset{+}{O}H$ for ether, etc.].

Let K_{keto} denote the equilibrium constant for reaction (1), i.e., the acidity constant of the keto form, and K_{enol} the same for reaction (2), i.e., for the enol form; the tautomeric equilibrium constant for the medium S or, what amounts to the same thing in this particular case, the enolization constant is designated as K_{TS}. Let us write the expressions for all the three constants:

$$K_{TS} = \frac{[A_{II}H]}{[A_IH]} \quad (3)$$

$$K_{keto} = \frac{[A^-]\,[\overset{+}{S}H]}{[A_IH]\,[S]} \quad (4)$$

$$K_{enol} = \frac{[A^-]\,[\overset{+}{S}H]}{[A_{II}H]\,[S]} \quad (5)$$

where the expressions enclosed in square brackets are the concentrations of the reagents.

* In solvents, such as benzene or hexane, which are incapable of adding a proton, the role of a Lewis base in the electrolytic dissociation of the enol and ketone is played by other molecules of the ketone or enol (autoprotolysis).

Let us now express the terms $[A_IH]$ and $[A_{II}H]$ in terms of the concentrations of the remaining components and constants:

$$[A_IH]=\frac{[A^-][\overset{+}{S}H]}{K_{keto}[S]} \quad \text{and} \quad [A_{II}H]=\frac{[A^-][\overset{+}{S}H]}{K_{enol}[S]}$$

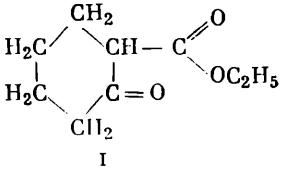
and substitute their values into Eq. (3):

$$K_{TS}=\frac{K_{keto}}{K_{enol}} \tag{6}$$

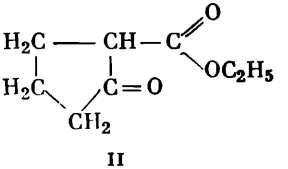
Expression (6) signifies that the enolization constant in the given solvent is equal to the ratio of the dissociation constant of the ketone to that (the solvent being the same) of the enol tautomer.* Thus, the higher the acidity constant of the keto form, K_{keto}, as compared with the acidity constant of the enol form, K_{enol}, the more strongly is the tautomeric equilibrium displaced to the side of the enol form, and vice versa.

From the data presented above it follows that the enol is more acidic in alcohols and benzene and much more acidic in water than the ketone; which means that the keto-enol equilibrium in these solvents lies nearly completely on the side of the keto form. The acidities of the two tautomers become closer in ether and reach an equilibrium in hexane. Hence, in principle, we deal here with the general regularity—the keto-enol equilibrium is shifted to the side of the less dissociated product.

The theory of the acid-base tautomeric equilibrium provides an explanation for the relation between acidity and enolizability. The older Claisen rule admitted the parallelism between the acidic properties and enolizability, i.e., meaning that the more "acidic" is the keto-enol form, the higher is the content of the enol form in the system. For example, acetylacetone, which is a stronger acid than acetoacetic ester, contains more of the enol form too. There are, however, a number of serious departures from the Claisen rule. For example, cyclohexanonecarboxylic ester (I) is a weaker acid than cyclopentanonecarboxylic ester (II) but is 76 per cent enolized, whereas the latter is only 4.5 per cent enolized:



I



II

* In a more general expression, the thermodynamic acidity constants must be taken and multiplied each by the corresponding activity coefficient of the undissociated tautomeric form in a given solvent. This expression will then give the tautomeric equilibrium constant for any solvent.

According to Kabachnik, the relation between acidity and enolizability can be accounted for rather simply. The tendency towards enolization depends on the ratio of the dissociation constants of the keto and enol forms, and acidity is governed by the absolute values of these constants.

The tautomerism in which the species that migrates in the course of a tautomeric change is a cation, is called **cationotropy**. A special, though the most important, case of cationotropy is **prototropy**. A special case of prototropy is the **keto-enol tautomerism**.

Table 4.6 presents a number of compounds which are capable of keto-enol tautomerism.

TABLE 4.6. **Equilibrium and Ionization Constants for Equilibrium Mixtures of Certain Keto-Enol Systems in Aqueous Solution**

(K_{TS} = tautomeric equilibrium constant; K_{ke} = ionization constant of the equilibrium mixture; K_k = ionization constant of the keto form; K_e = ionization constant of the enol form)

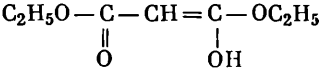
Compound	Literature data		Data * obtained by Kabachnik	
	K_{TS}	K_{ke}	K_k	K_e
Acetone	2.5×10^{-6}	1.6×10^{-15}	1.6×10^{-15}	6.4×10^{-10}
Ethyl acetoacetic ester	9.2×10^{-4}	1.8×10^{-13}	1.8×10^{-13}	2.0×10^{-10}
Cyclopentanonecarboxylic ester	0.002	2.1×10^{-11}	2.1×10^{-11}	1.0×10^{-8}
Acetoacetic ester	0.004	2.1×10^{-11}	2.1×10^{-11}	5.3×10^{-9}
2 Methylindanedione	0.011	7.1×10^{-7}	7.2×10^{-7}	6.5×10^{-5}
Methylacetylacetone	0.016	1.5×10^{-11}	1.5×10^{-11}	1.0×10^{-9}
Cyclohexanonecarboxylic ester	0.048	1.4×10^{-13}	1.4×10^{-13}	3.2×10^{-12}
Bromoacetylacetone	0.081	1.0×10^{-7}	1.1×10^{-7}	1.4×10^{-6}
Acetylcyclopentanone	0.178	1.5×10^{-8}	1.8×10^{-8}	1.0×10^{-7}
Acetylacetone	0.22	1.2×10^{-9}	1.4×10^{-9}	6.5×10^{-9}
Acetylcyclohexanone	0.41	8.1×10^{-11}	1.2×10^{-10}	2.8×10^{-10}
Benzoylacetone	0.48	2.0×10^{-9}	3.0×10^{-9}	6.2×10^{-9}
Formylcyclopentanone	0.68	1.5×10^{-6}	2.5×10^{-6}	3.7×10^{-6}
Formylcyclohexanone	0.94	4.5×10^{-7}	8.7×10^{-7}	9.2×10^{-7}
Dimedone	20.3	5.6×10^{-6}	1.2×10^{-4}	6.0×10^{-6}

* The calculations were made according to the formula:

$$K_e = \frac{K_{ke}(K_{TS}+1)}{K_{TS}} \quad \text{and} \quad K_k = K_{ke}(K_{TS}+1)$$

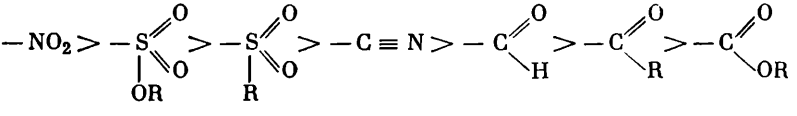
The much stronger tendency of diketones towards enolization as compared with the esters of β-keto acids should be noted. This can probably be accounted for by the greater ability of the carbonyl group, as compared with the carbalkoxy group, to undergo conjugation with the double bond of the enol (the greater $-T$ effect).

In malonic ester, on the contrary, both the electrolytic dissociation and enolization occur to a small extent, despite the strongly ionizable hydrogen atom, which is even directly replaced by a metal under the action of metallic sodium. This means that in the enol form of malonic ester

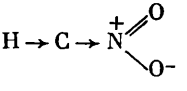


the hydrogen atom of the enol is relatively more acidic. Such is evidently the influence of the neighbouring ethoxy group.

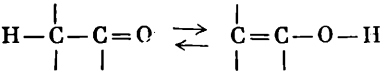
According to the acid-enhancing, electron-withdrawing effect on the adjacent CH_2 linkage (the negative inductive or $-I$ effect, see Volume I) the various functional groupings can be arranged in the following sequence (Arndt):



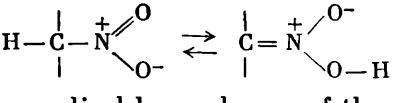
In other words, the groups in this series are arranged in order of decreasing tendency (from left to right) to draw electrons away from the CH linkage in systems of the type



and thereby to enhance the acidity of the hydrogen atom. This ability, however, shows no parallelism with the tendency of the proton towards migration to oxygen (or to nitrogen in the —C≡N group) according to schemes of the following types:



or



If the hydrocarbon radical has only one of the substituents of the above series, then the R—CH_2—A form (where A is the functional substituent) is invariably much less acidic than the tautomeric form R—CH=AH, in which the proton has migrated to the oxygen or nitrogen of the group A. The equilibrium in such monofunctional

compounds is so far to the side of the $R-CH_2-A$ form that the presence of the $R-CH=AH$ forms may be ignored. But if a second substituent from the same series is introduced into the β-position relative to A, then in the resulting system of the type

$$-\overset{\overset{O}{\|}}{C}-CH_2-\overset{\overset{O}{\|}}{C}- \quad \text{or} \quad -\overset{\overset{O}{\|}}{C}-CH_2-NO_2 \quad \text{or} \quad -\overset{\overset{O}{\|}}{C}-CH_2-C\equiv N$$

the protons of the methylene group become much more acidic than those in a monofunctional compound and may be comparable in acidity with the protons of a tautomeric form:

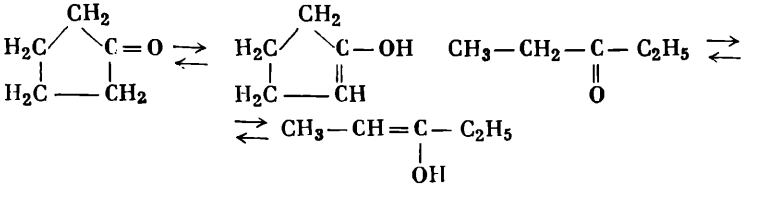
$$-\underset{\underset{OH}{|}}{C}=CH-\overset{\overset{O}{\|}}{C}- \qquad -\underset{\underset{OH}{|}}{C}=CH-NO_2 \qquad -\underset{\underset{OH}{|}}{C}=CH-C\equiv N$$

and so on.

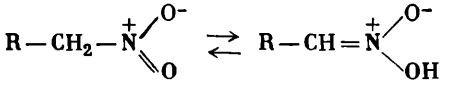
Besides, as has already been pointed out, the tautomeric form is stabilized by a decrease in the energy level due to the conjugation of the multiple bonds C=C and C=O, C=C and N=O or C=C and C≡N. The tendency towards enolization and the acidity therefore increase. The acidity of the C—H form of a tautomeric substance is mainly determined by the acid-enhancing effect of substituents on the carbon-hydrogen bonds, while the tendency towards enolization is chiefly governed by the ability of A groups to add a proton with the formation of an enolic system of bonds.

In a qualitative determination of the position of equilibrium based on the structure of a tautomeric substance, one must take into account the effect of substituents (both the inductive and tautomeric effects) in the two tautomeric forms.

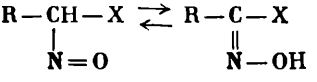
There is still another factor—the entropy factor. The more degrees of freedom of rotation and conformational change in the molecule, the higher is its entropy. Any fixation of the form is associated with the decrease of entropy. The appearance of a double carbon-carbon (C=C) bond in the enol with a rigid planar arrangement of the substituents at the olefinic carbon tends to reduce the entropy. The probability is thus against enolization. But in systems which are inherently rigid (for example, in small rings, such as, say, in cyclopentanone) such a fixation has already taken place and the enolization will not cause an additional decrease of the entropy. Therefore, in rigid forms the enolization is relatively higher than in mobile forms, say, it is greater in cyclopentanone than in pentanones:



Let us also recall other prototropic tautomeric systems which we have already encountered. These are the **nitro-aci-nitro tautomerism** say,

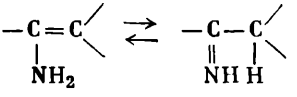


nitroso-oxime tautomerism:

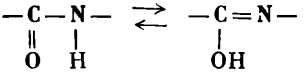


where X = —C(=O)—R or $-NO_2$ (in alkylnitrolic acids, see Volume I).

Absolutely analogous with keto-enol tautomerism is **imine-enamine tautomerism** which is not of great importance:

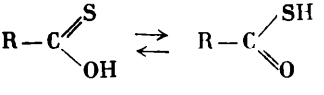


and the widespread **lactam-lactim tautomerism** (A. Baeyer):

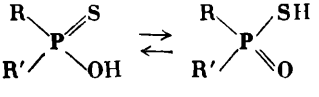


which will be considered in a section dealing with heterocycles (Volume III).

Mention should also be made of the **thiono-thiol tautomerism** of thiocarboxylic compounds:



which has been studied in recent years by M. I. Kabachnik, S. T. Yoffe and Yu. N. Sheinker, and also of the analogous tautomerism of thiohydroxy acids of phosphorus (M. I. Kabachnik and T. A. Mastryukova):



All these types of tautomerism, including keto-enol tautomerism, are called **triad tautomerism**, since the entire tautomeric change—the proton transfer and the migration of double bonds—takes place between three atoms: the triad C—C=O in the case of keto-enol tautomerism and the triads printed in boldface in the other cases of tautomerism given above

There also exists the **diad tautomerism**. Examples are: the tautomerism of hydrocyanic acid

$$H-C\equiv N: \rightleftarrows :C\equiv N-H$$

and the tautomerism of phosphorous acid and its derivatives:

$$H-\underset{\displaystyle OC_2H_5}{\overset{\displaystyle OC_2H_5}{\underset{|}{\overset{|}{P}}}}=O \rightleftarrows :\underset{\displaystyle OC_2H_5}{\overset{\displaystyle OC_2H_5}{\underset{|}{\overset{|}{P}}}}-OH$$

In such cases the tautomeric transformation occurs between two atoms: C and N in the first and P and O in the second case. It can easily be seen that, in contrast to the triad tautomerism, diad tautomerism is inevitably associated with the change of the valency of one of the atoms involved (C and P in our examples).

There are also **pentad systems** and even more complicated tautomeric systems which are not considered in this book. In fact, prototropy covers almost everything known of cationotropic tautomerism. It was only around 1960 that D. N. Kravtsov discovered the previously unknown **metallotropy** while studying cyclic systems, including a skeleton of the type:

$$N-C=C-C=C \rightleftarrows N=C-C=C-C$$
$$\quad\|\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\|$$
$$\quad O\quad\quad\quad\quad\quad OHgR\quad\quad\quad\quad OHgR\quad\quad\quad\quad O$$

where R is an aromatic radical, and the four carbon atoms joined into a conjugated system enter into the composition of the benzene ring.

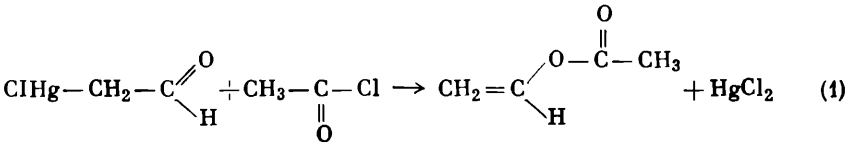
This type of prototropy (H in place of HgR) has long been known. It is an example of **heptad tautomerism**.

Ordinarily, the metallic derivatives of tautomeric systems are not tautomeric, but they possess dual reactivity, just like the tautomeric systems themselves. Before taking up the consideration of the well-known substances of this kind—sodium enolates of the various types, which also include sodioacetoacetic ester (page 76), mention should be made of the mercury derivatives of carbonyl compounds obtained around 1950 (A. N. Nesmeyanov, I. F. Lutsenko). Substances of the types (I) and (II) are not tautomeric:

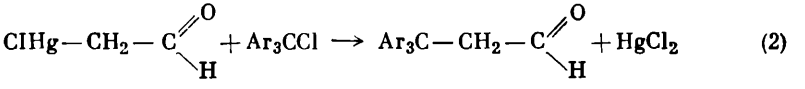
$$\underset{\text{I}}{ClHgCH_2-C(=O)H} \not\rightleftarrows CH_2=C(OHgCl)H$$

$$\underset{\text{II}}{ClHgCH_2-C(=O)-CH_3} \not\rightleftarrows CH_2=C(OHgCl)-CH_3$$

and have a carbonyl structure, which is proved by the absence of mercury ions in solutions and by the negative test for a carbon-carbon double bond. But these compounds exhibit dual reactivity: in some cases they react like aldehydes and ketones and more often like enolic compounds. Below are given examples of the both types of reactions:



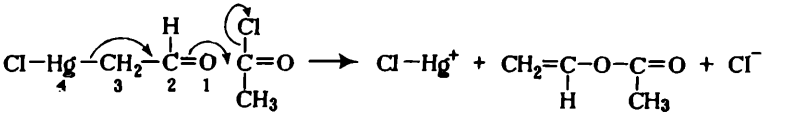
(1)



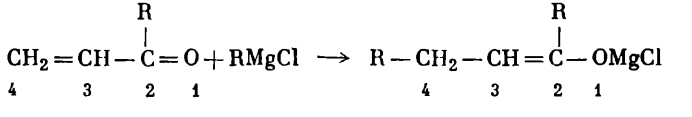
(2)

where Ar is an aromatic radical, say, the benzene residue—phenyl, C_6H_5.

The point here is that in reaction (1) which involves the **reaction-centre transfer** (the carbon attached to the metal should have been the normal centre of acylation), the electrophilic attack of the carbonyl carbon of acetyl chloride is directed to the oxygen. This is facilitated by the fact that the strongly polarizable Hg—C bond can easily supply an electron pair to the neighbouring C—C bond and thus compensate for the loss of the electron pair of the broken C=O bond (the curved arrows below indicate the migration of an electron pair):



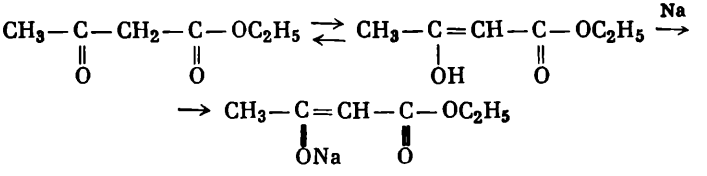
In principle, such an interaction between Hg—C and C=O bonds shows many points of analogy with the conjugation of double bonds (π,π-conjugation), say, in the C=C—C=O system (see Volume 1, page 401) and may be called the σ,π-conjugation or **hyperconjugation**. Indeed, from the example given above it is seen that the acylation products of chloromercuroacetaldehyde are formed as a result of the 1,4-addition, which is similar to the addition, say, of a Grignard reagent to unsaturated ketones in the 1,4-positions



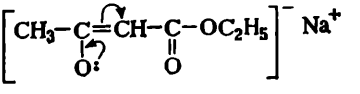
in the sense that in both systems the 1,2 and 3,4 bonds are broken and a multiple 2,3 bond is formed. The only difference is that in the case of the 1,4-addition to the π,π-conjugation system the entire

molecule remains bound (since only the double bonds are broken) and in the 1,4-addition to the σ,π-conjugated system not only the 1,2 double bond is disrupted, but the single 3,4 bond (a σ-bond) as well. Therefore, the reaction results in the formation of two distinct molecules. Thus, the reaction-centre transfer is associated with the conjugation of π,π-bonds or σ,π-bonds.

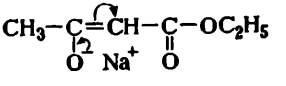
An analogous situation is observed in the case of the dual reactivity of sodium derivatives of carbonyl-enol systems. There is no doubt that sodioacetoacetic ester, for example,



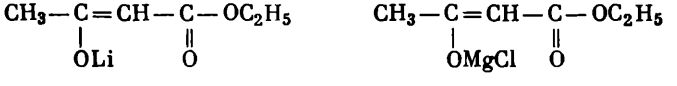
has an enolate structure, which is in all probability close to the ionic structure, or is an ionic compound. In this case the anion is mesomeric, i.e., its electrons are but slightly shifted in the direction shown by curved arrows since oxygen is more electronegative than carbon:



In non-polar or slightly polar media the sodium cation evidently forms an ionic pair with the oxygen of the enolate anion:



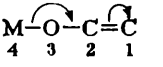
In the case of lithium and, more often, of magnesium, which exhibit the greater tendency towards the formation of covalent bonds with oxygen, the formulas of the metallic derivatives are more correctly represented with a covalent, though strongly polarized, O—M bond:



But sodioacetoacetic ester and the other metallic derivatives mentioned above are alkylated not at oxygen but at carbon, i.e.,

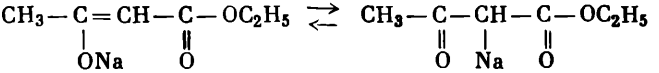
with a reaction-centre transfer*:

When the electrophilic particle CH_3—I attacks the carbon, the bond system



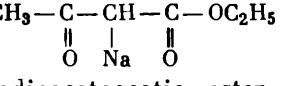
behaves, consequently, as σ,π-conjugation system supplying the required electron pair for the formation of a new bond with the methyl group at the expense of the single 3,4 bond which is broken. Thus, this is also an 1,4-addition across the conjugated bond system.

It has been suggested that sodioacetoacetic ester is tautomeric, namely, metallotropic:



I II

and that the tautomeric form (II), which is not detectable because of the negligible concentration, is responsible for the alkylation at carbon. Systems of this kind, in which tautomerism is expected on account of their dual reactivity but the second tautomer cannot be actually isolated or detected, have come to be known as **pseudomeric**. From this standpoint



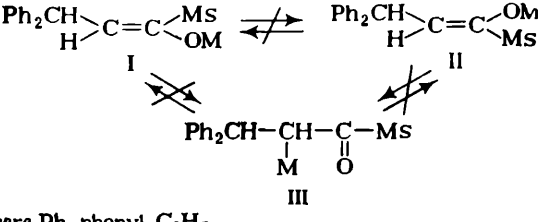
is a pseudomer of sodioacetoacetic ester.

Pseudomerism has been rejected at present. In the many cases of the formerly supposed pseudomerism we can prove the absence of a pseudomer, despite the ability of the molecule to react also according to the presumed pseudomeric structure, as we have just seen for chloromercuroacetaldehyde. This will be illustrated once more at a later time by a concrete example. At this point, a general conclusion may be made: had the pseudomer been present in undetectable trace amounts, the rate constant of the reaction proceeding via this pseudomer should have been enormously and unprecedentedly great in order to compensate for the smallness of the pseudomer concentration (M. I. Kabachnik). The point is that the reaction

* Kabachnik and Yoffe have recently found that the direction of the alkylation of sodioacetoacetic ester and, especially, of sodium acetylacetonate, is changed in the presence of steric hindrances. For example, sodium acetylacetonate with secondary propyl iodide gives 27 per cent of the O-*sec*-propyl derivative, and with secondary butyl iodide, 35 per cent of the O-*sec*-butyl derivative.

rate is proportional to the rate constant and to the concentration of the reagent.*

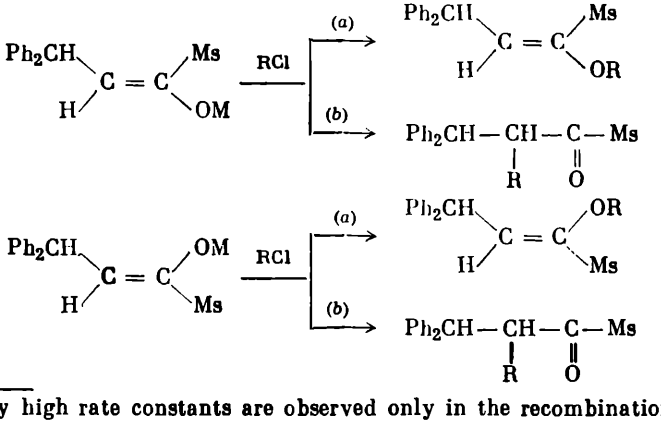
A. N. Nesmeyanov and V. A. Sazonova have succeeded in showing that the metal enolates that follow exhibit no keto-enolate tautomerism, and that the enolates nevertheless display dual reactivity. It has been demonstrated as follows. The *cis*- and *trans*-isomeric enolates (I) and (II) prepared with the aid of a Grignard reagent (or organolithium or organosodium compounds) are stable under certain conditions and incapable of interconversion. This proves that they cannot be transformed into the keto form (III) either, otherwise the *cis-trans* conversion would have occurred via that keto form:



where Ph-phenyl, C_6H_5

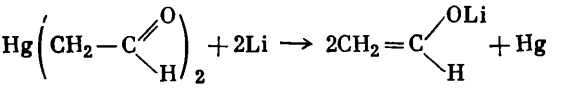
Ms-mesityl, $C_6H_2(CH_3)_3$

In reactions of alkylation and acylation of *cis*- and *trans*-forms (I) and (II), however, either of them is capable of forming derivatives of the corresponding structure and configuration and also derivatives of the keto form (III), i.e., is capable of entering into a reaction with the reaction-centre transfer. Reactions of the type (*a*) take place if $R=-\overset{\overset{O}{\|}}{C}C_6H_5$ and reactions (*a*) and (*b*) proceed concurrently when $R=-CH_2OCH_3$:

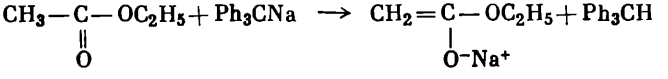


* Very high rate constants are observed only in the recombination of ions or radicals.

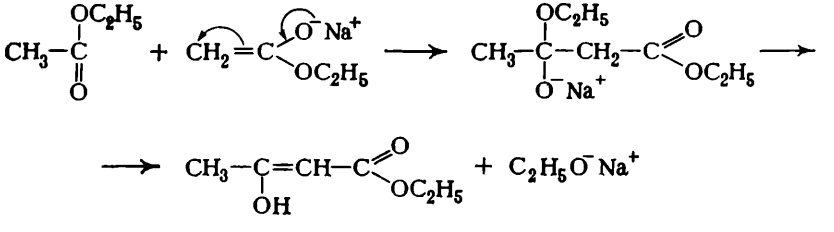
The simplest conceivable enolate is the lithium enolate of acetaldehyde, $CH_2=CH-OLi$, which has been obtained by A. N. Nesmeyanov and I. F. Lutsenko also by a reaction involving the reaction-centre transfer:



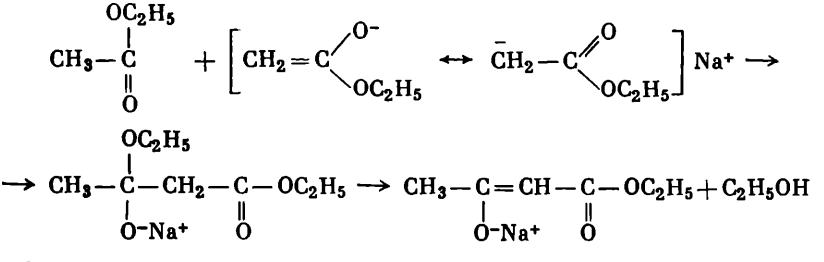
If ethyl acetate is allowed to react with triphenylmethylsodium, $(Ph)_3CNa$, a sodium derivative of ethyl acetate can be produced:



It is precisely this enolate (which can also be made by the action of sodium ethoxide or metallic sodium on ethyl acetate) that serves as a reagent in the formation of acetoacetic ester by the Geuther-Claisen reaction which proceeds with transfer of the reaction centre. This reaction may be represented in the following form:

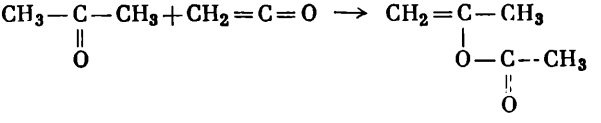


Such an interpretation emphasizes that the reaction of the sodium enolate of an ester involves the transfer of the reaction centre and is an extension of the generally recognized Arndt's viewpoint on the mechanism of ester condensation (page 71), assuming that ethyl acetate is attacked by the mesomeric anion:

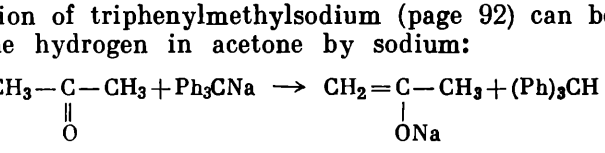


There arises a question: Are the simplest aldehydes and ketones able to react in a dual manner and with the formation of precisely the derivatives of enol forms, and not via the tautomeric enol, whose

content is too low, but with the transfer of the reaction centre? Such reactions are known to have taken place. For example, ketene acylates acetone according to the equation:

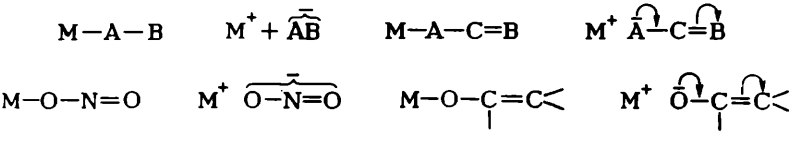


The action of triphenylmethylsodium (page 92) can be used to replace the hydrogen in acetone by sodium:



The grouping H—C—C=O, like the one discussed above (IIg—C—C=O), contains a system of σ,π-conjugated bonds, but the conjugation is here less pronounced and a more powerful electrophilic reagent is required to make it reveal itself.

Hence, the metallic derivatives of diad and triad tautomeric systems can enter into reaction either in the dissociated state or in the form of molecules; in either case they are attacked by an electrophile. Let us denote the terminal atoms of a diad or triad by A and B, the central atom of the triad by C, and the metal by M. The lower line gives concrete examples illustrating these schemes:



A question may be asked: What factors contribute to the occurrence of a reaction without transfer of the reaction centre (i.e., a reaction at the atom with which the metal is bound or from which it separates on dissociation) and what factors are responsible for the transfer of the reaction centre (i.e., for the attack on the other terminal atom of the tautomeric diad, triad and so on)?

A. N. Nesmeyanov and M. I. Kabachnik formulated the following rules for keto-enol and lactam-lactim triads:

1. If the M—O bond is strongly ionized and the reagent used is a cation or a powerful electrophilic molecule, a rapid O-reaction takes place. This may be exemplified by the following reactions: the Claisen O-acylation (i.e., by an acid chloride in pyridine solution); other alkylation reactions initiated by quaternary ammonium cations; the O-acylation of sodioacetoacetic ester by chlorocarbonate ester.

2. If the O—M bond is not ionized at all or slightly ionized and the reagent used is strongly electrophilic, the O-reaction proceeds more slowly; the C-reaction with transfer of the reaction centre begins to predominate. This course is followed by the reaction between the chelate copper derivative of the enol of acetoacetic ester and chlorocarbonate ester.

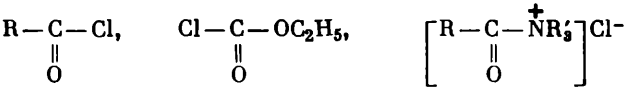
3. The same result is observed in the reverse case, when the reagent is a weak electrophile but the O—M bond is strongly ionized. Such are the reactions of alkylation (better, in ionizing media), by alkyl halides, of sodium enolates and sodium derivatives of lactam-lactim triads or the corresponding acylation reactions.

4. In case the O—M bond is unionized and the reagent is weakly electrophilic, there also takes place an O-reaction, which however proceeds slowly in this case, possibly via the four-membered transition state. An example is the O-alkylation of the silver salts of keto-enols and lactam-lactims by alkyl halides.

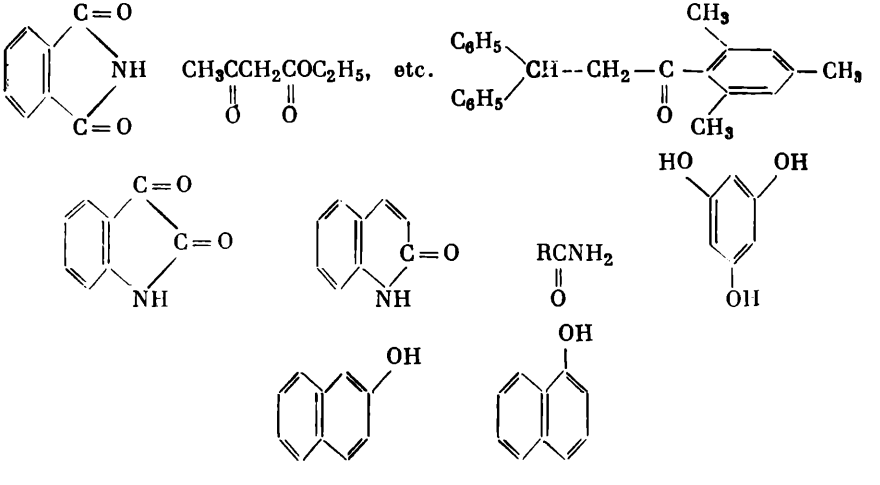
Below are given a number of alkylating agents which are arranged in order of increasing electrophilic power:

$$RI,\ R_2SO_4,\ CH_2{=}CH{-}CH_2Cl,\ C_6H_5Br,\ CH_3OCH_2Cl,\ R_3\overset{+}{O}\ BF_4^-,$$
$$(C_6H_5)_2CCl_2,\ (C_6H_5)_3CCl,\ (nO_2NC_6H_4)_3CBr$$

Some acylating agents are given below in the same sequence:



As regards the triad tautomeric systems themselves, they may be arranged in the following sequence in order of increasing tendency for their sodium derivatives to enter into O-reactions:



This series may be regarded as a sliding-scale with respect to each of the preceding ones. An alkylating electrophile sufficiently strong for the beginning of the series will be found to be weak for its end.

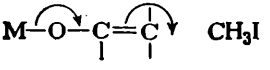
The general rules are as follows:

1. In the free anion of a tautomeric compound, no matter whether it is a keto-enol or lactam-lactim, the δ-charge is sharply predominant on the more electronegative oxygen. If the electrophilic agent used is one of the following cations

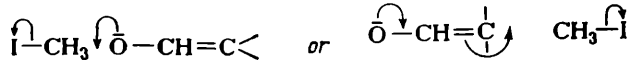
$$(CH_3)_3C^+, \qquad (C_6H_5)_3C^+, \qquad R-\overset{\overset{O}{\|}}{C}{}^+$$

the fast reaction will proceed as an ionic recombination, i.e., at oxygen.

2. If the M—O bond is not ionized, the metal shields the approach to the oxygen and the reaction takes place at the accessible, unshielded carbon (or nitrogen), which is supplied with electrons due to the $+T$ effect:



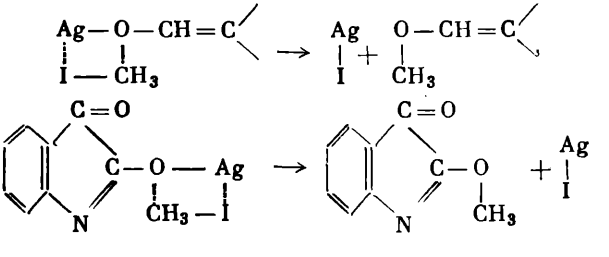
3. In the reverse case, when the electrophile is weak and the M^+O^- bond is ionic, the carbon (or nitrogen) being attacked all the same, it may be said that an interaction of the type



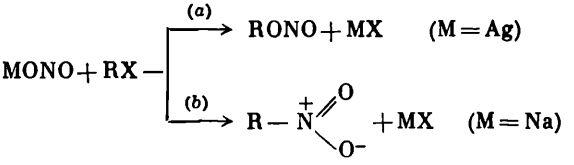
requires, for the transition state, that both reagents be well polarizable in the direction indicated by the arrows. The two molecules can however be made polarized only in the case of the right-hand scheme, which means that the carbon is attacked due to the $+T$ effect of the enolate anion. The left-hand scheme is either unfeasible because of the low polarizability of the oxygen atom or would be possible only under more vigorous conditions, say, in the reaction

$$CH_3I + NaOH \longrightarrow CH_3OH + NaI$$

4. The fourth case is illustrated by the following schemes:



Similar factors govern the alkylation of the metal salts of diad tautomers (N. Kornblum):



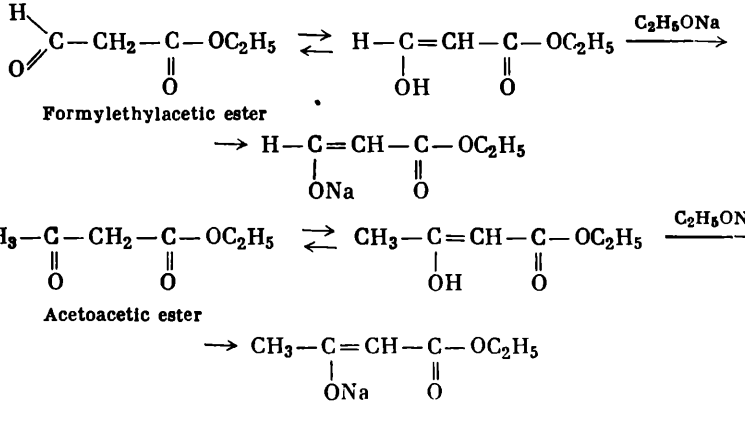
The rule of dual reactivity was most briefly formulated by Pearson, who classified all reagents and molecular fragments of systems exhibiting dual reactivity into "hard" (i.e., strongly polar, but difficultly polarizable) and "soft" (i.e., weakly polar, but easily polarizable). Pearson's rule states: hard-likes-hard and soft-likes-soft.

In many cases, the direction of dual reactivity also depends on other factors: the solvating power of the solvent, its dielectric constant, the heterogeneity or homogeneity of the medium, steric factors.

A solvent that strongly solvates an electrophile reduces the electrophilic power of the latter with all the attending consequences. If the solvent strongly solvates the oxygen of the triad (strong hydrogen bonding) and thereby shields it, the reaction is directed to the other end of the triad. The same effect is exerted by the formation of ion pairs in non-polar media or by the heterogeneity of the medium (Kornblum).

B. Esters of β-Aldehydic and β-Ketonic Acids

As has already been shown, the esters of β-aldehydic and β-ketonic acids when reacted with a sodium alkoxide in alcoholic solution are converted into sodium enolates. For example,



These enolates are widely employed in syntheses involving the formation of new carbon-carbon bonds. Almost all reactions of such sodium derivatives with the various compounds RX, where R is any organic radical and X is a sufficiently mobile halogen joined to carbon, proceed at the carbon atom. This can be exemplified by some of the reactions of sodioacetoacetic ester with RX, where R = $-CH_3$, $-C_2H_4Cl$, $-CH_2-COOC_2H_5$, the reaction product being then subjected to ketonic or acid cleavage (page 78):

I. $CH_3-C(ONa)=CH-C(=O)-OC_2H_5 + CH_3I \rightarrow CH_3-C(=O)-CH(CH_3)-C(=O)-OC_2H_5 + NaI$

$CH_3-C(=O)-CH(CH_3)-C(=O)-OC_2H_5 \xrightarrow[-C_2H_5OH]{Na^+OH^-;\ H_2O} CH_3-C(=O)-ONa + CH_2(CH_3)-C(=O)-ONa$

$\downarrow H^+;\ H_2O$

$CH_3-C(=O)-CH(CH_3)-C(=O)-OH \xrightarrow[-CO_2]{} CH_3-C(=O)-CH_2-CH_3$

II. $2CH_3-C(ONa)=CH-C(=O)-OC_2H_5 + ClCH_2-CH_2Cl \xrightarrow[-2NaCl]{}$

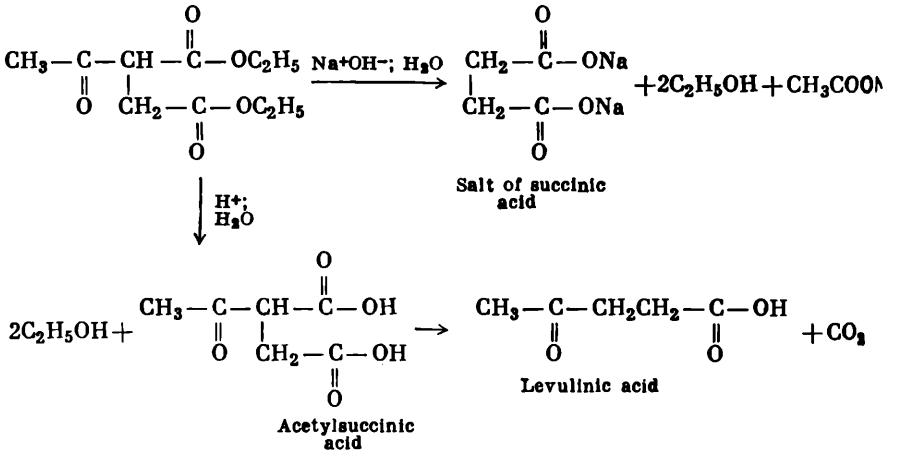
$\rightarrow$ [$CH_3-C(=O)-CH(-CH_2-CH_2-)-C(=O)-OC_2H_5$] $\xrightarrow{Na^+OH^-;\ H_2O}$

$\xrightarrow{-2CH_3COONa;\ -2C_2H_5OH}$ $NaO-C(=O)-(CH_2)_4-C(=O)-ONa$ Salt of adipic acid

$\xrightarrow[-2CO_2;\ -2C_2H_5OH]{H^+;\ H_2O}$ $CH_3-C(=O)-(CH_2)_4-C(=O)-CH_3$ 2,7-Octanedione

III. $CH_3-C(ONa)=CH-C(=O)-OC_2H_5 + ClCH_2-C(=O)-OC_2H_5 \xrightarrow[-NaCl]{}$

$\rightarrow CH_3-C(=O)-CH(CH_2-C(=O)-OC_2H_5)-C(=O)-OC_2H_5$



By comparing the compounds obtained by the acid cleavage of the alkylation products of sodioacetoacetic ester with substances resulting from the alkylation of sodiomalonic ester followed by subsequent decarboxylation of the substituted acid (see Volume I, page 254), we find them to be identical. But the ketonic cleavage of acetoacetic ester offers new possibilities for the synthesis of ketones, polycarbonyl compounds, ketonic acids, etc. Since ester condensation can give a great variety of esters of β-ketonic acids of open-chain and cyclic structure, with one or two carbonyl groups, and one or two carboxyl groups, and these esters can be introduced into the Michael reaction, it becomes clear that the alkylation of the sodium derivatives of all these structures with the subsequent ketonic or acid cleavage offers an extremely versatile and powerful method of building up carbon skeletons to the organic chemist.

The synthesis of ketones and acids via the esters of β-ketonic acids must be regarded as an addition to the other previously studied methods of synthesizing these types of compounds.

4.4. Hydroxyaldehydes and Hydroxyketones

The simplest hydroxycarbonyl compounds (aldehydic and ketonic alcohols) are listed in Table 4.7. These compounds can be synthesized by the general methods of introducing a hydroxyl group into carbonyl compounds and a carbonyl group into hydroxyl-containing compounds. For example, glycolic aldehyde can be made by the oxidation of glycol:

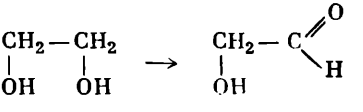
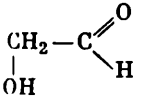
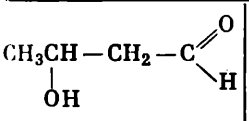
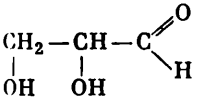
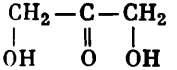
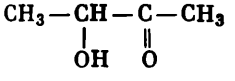
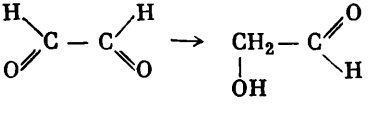


TABLE 4.7. **Hydroxyaldehydes and Hydroxyketones (Aldehydic and Ketonic Alcohols)**

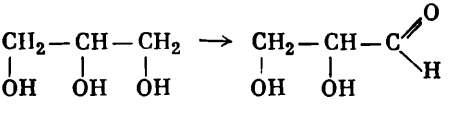
Formula	Name	m. p., °C	b. p., °C	Density d
	Glycolaldehyde	97	—	1.366 (at 100°C)
	Aldol (β-hydroxybutyraldehyde or 3-hydroxybutanal)	Syrup	83 (20 mm Hg)	1.103 (d_4^{20})
	Glyceraldehyde	138; 145	140-150 (0.8 mm Hg)	1.455 (d_{15}^{18})
	Dihydroxyacetone	89*	—	—
	Acetoin (3-hydroxy-2-butanone)	15	148	1.002 (d_4^{15})

* Crystallizes in the form of a dimer.

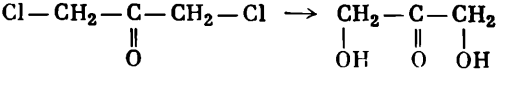
or by the partial reduction of glyoxal:



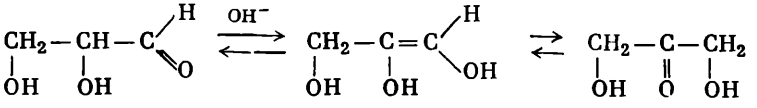
Glyceraldehyde is produced by the partial oxidation of glycerol:



and dihydroxyacetone is made by the hydrolysis of 1,3-dichloroacetone:

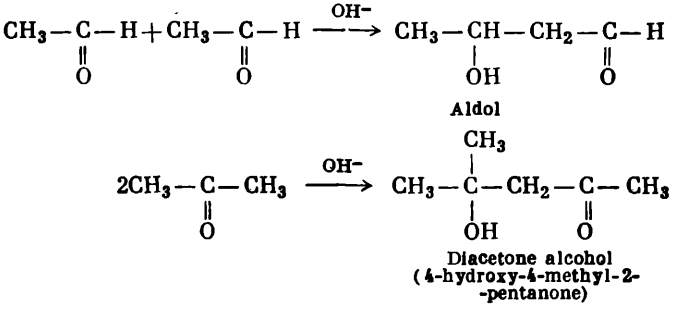


Glyceraldehyde and dihydroxyacetone are capable of interconversion in alkaline medium as a result of enolization:

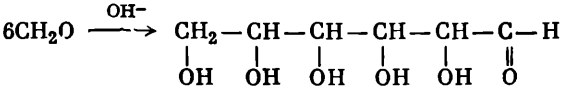


Such an interconversion (upon the attainment of equilibrium) is typical of all α,β-hydroxycarbonyl compounds.

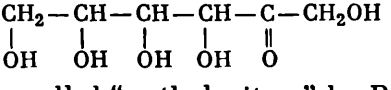
The aldol condensation leads to β-aldehydic and β-ketonic alcohols:



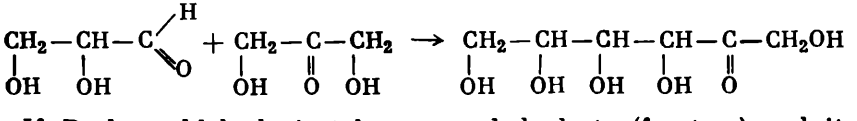
Another type of condensation discovered by A. M. Butlerov makes it possible to convert formaldehyde in aqueous solution under the influence of lime water into a mixture of isomeric and stereoisomeric hexoses, i.e., pentahydroxymonocarbonylhexanes, which belong to the class of sugars and will be discussed in detail later:



and



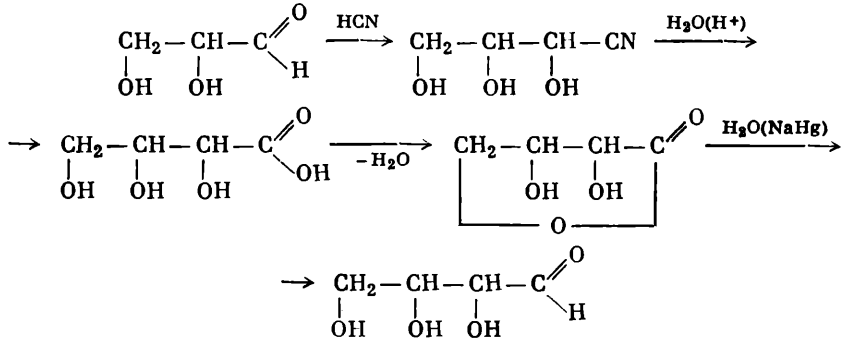
(This mixture was called "methylenitane" by Butlerov, and Emil Fischer isolated "acrose"—the racemate of fructose—from this mixture.) The same result obtains in the aldol condensation of glyceraldehyde with dihydroxyacetone:



If D-glyceraldehyde is taken, a carbohydrate (fructose) and its diastereomer (sorbose) are obtained, the amount of the latter being somewhat less than that of the former. If the starting material is

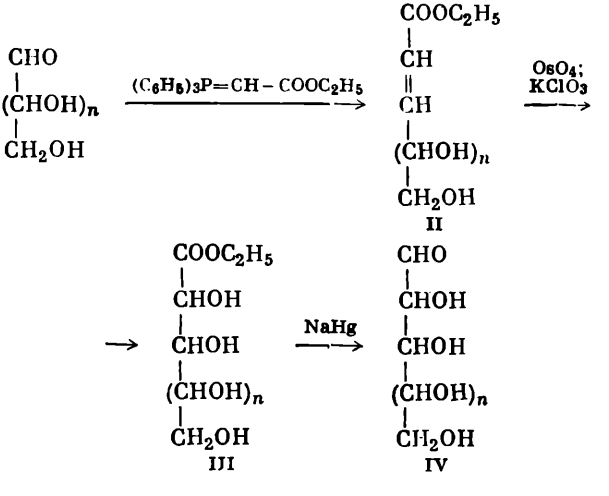
racemic glyceraldehyde mixed with dihydroxyacetone (this mixture is prepared by the careful oxidation of glycerol and is called glycerose), the same Butlerov and Fischer product (acrose) results.

Of essential importance for the understanding of what follows is the method of building up hydroxyaldehydes, which leads to hydroxyaldehydes containing one CHOH linkage more in the chain. This method consists of the addition of hydrocyanic acid to a hydroxyaldehyde, the hydrolysis of the resulting hydroxynitrile to a hydroxy acid and the reduction of the ester or lactone of this hydroxy acid to a hydroxyaldehyde. As an example, we give the building up of the chain of glyceraldehyde:



Note that the reaction gives rise to a new asymmetric carbon atom in the alpha-position relative to the aldehyde group.

A new method of building up hydroxy- and polyhydroxyaldehydes by two CHOH units through the use of the Wittig reaction (see Volume I, page 335) has been devised by N. K. Kochetkov and B. A. Dmitriev:



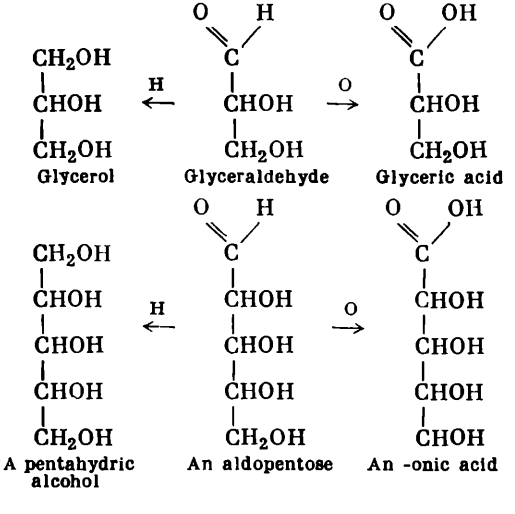
Hydroxyaldehyde (I) reacts with triphenylphosphine carbethoxymethylene, forming an unsaturated acid (II) with a *trans*-configuration. The double bond in the unsaturated acid can be hydroxylated (for example, by the action of OsO_4) and the resulting ester of the polyhydroxycarboxylic (aldonic) acid (III) is reduced by sodium amalgam to polyhydroxyaldehyde (IV) which has two carbon atoms more than the parent compound.

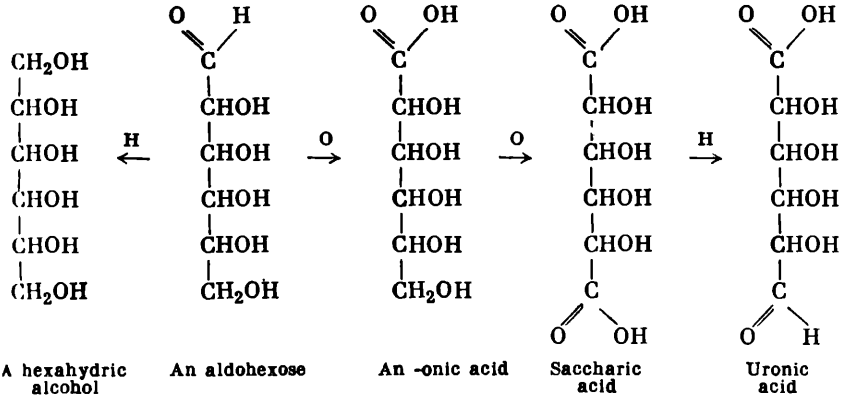
The method enables the building up of two carbon links and the adjustment of the stereochemistry of the asymmetric centres being formed.

A. Properties of Hydroxyaldehydes and Hydroxyketones

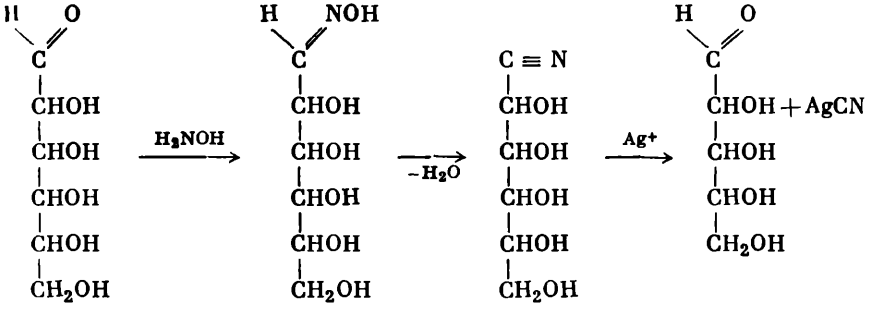
It is natural that hydroxyaldehydes and hydroxyketones (aldehydic and ketonic alcohols) enter into many of the reactions which are already familiar to us, by their alcoholic and aldehydic or ketonic groups. These reactions will not be considered here unless they are needed for further discussion.

For example, the alcoholic groups of hydroxyaldehydes and hydroxyketones are acetylated by acetic anhydride and from the amount of the latter consumed one can deduce the number of hydroxyl groups in the molecule. Primary alcoholic groups can be oxidized to aldehydic and then to carboxyl groups. Aldehydic groups can be reduced to primary alcoholic, and ketonic to secondary alcoholic groups. All these reactions establish the close relations between hydroxycarbonyl compounds and hydroxy acids and polyhydric alcohols. These relations may be illustrated by the example of the structures of glyceraldehyde, tetrahydroxypentanal (aldopentose) and pentahydroxyhexanal (aldohexose), without going, for the time being, into the stereochemical relationships (see the scheme)





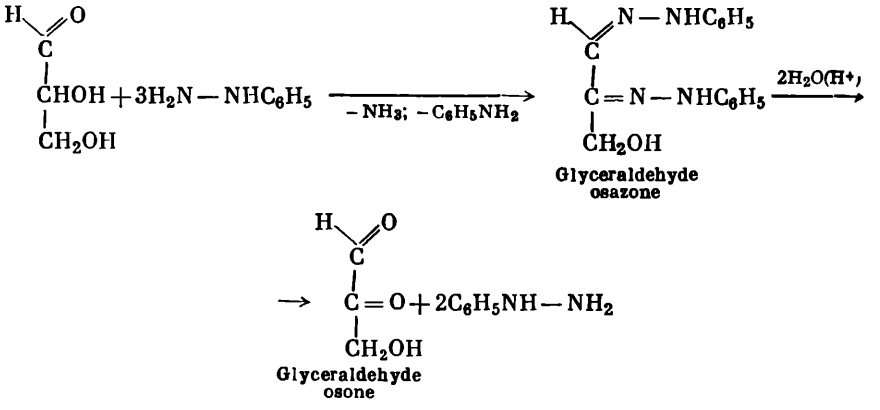
Reactions between hydroxyaldehydes and hydroxylamine are important. The oximes resulting from such reactions are converted into nitriles by the action of dehydrating agents; from the nitriles formed it is possible to remove HCN by a silver ion to obtain a hydroxyaldehyde which has one CHOH link less:



All these reactions are not novel to us, but with their aid it is possible to accomplish an important transformation from a hexose to a pentose or from a pentose to a hydroxyaldehyde with three alcoholic linkages, or finally, from the last compound to glyceraldehyde.

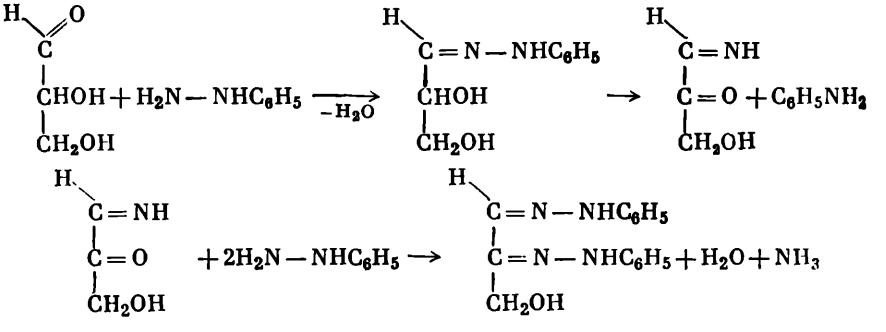
The reaction of hydroxyaldehydes with phenylhydrazine takes a different course than for ordinary aldehydes. So-called **osazones** are formed (E. Fischer), which are yellow crystalline substances and which are converted on acid hydrolysis into **osones**—hydroxyketo-

aldehydes:

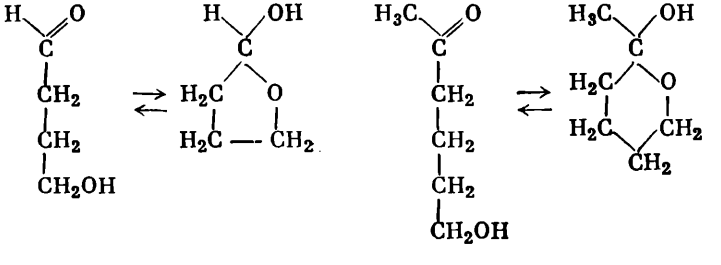


Osazones are the *bis*-phenylhydrazones of osones.

The mechanism of this unusual and important reaction has been elucidated by M. M. Shemyakin and may be represented by the following scheme:



γ- and δ-Hydroxycarbonyl compounds present a new type of prototropic tautomerism which is called the **exo-ring tautomerism** and consists in that an open form exists in equilibrium with a cyclic form, which usually strongly predominates:



4.5. Carbohydrates

Compounds of the composition $C_5H_{10}O_5$, $C_6H_{12}O_6$, $(C_6H_{10}O_5)_x$, $C_{12}H_{22}O_{11}$, which are explicitly in close chemical relations, are widely distributed in living nature. For example, the last two types are converted into the second compound by hydrolysis. They are all characterized by a number of similar reactions. Since the composition of such compounds was believed to be represented by the general empirical formula $C_n(H_2O)_m$, they were called **carbohydrates*** (Schmidt, 1844), and this name has survived, though it has no chemical meaning.

The carbohydrates are the simple **sugars** or **monosaccharides** (ordinary beet, or cane, sugar—saccharose or sucrose; grape sugar—glucose; fruit sugar—fructose; milk sugar—lactose), starch, glycogen, and cellulose, from which the walls of plant cells are built (hence the name cellulose) and which is in an almost pure state in the form of cotton wool and filter paper, or in the combined state (with lignin) in the form of wood.

Plants contain polysaccharides which are high-molecular-weight polymers built up by repeated condensations of monosaccharides (monoses) and which are formed from the latter by loss of water and are thus anhydrides or ether derivatives of the monosaccharides. The hydrolysis in acid medium converts them into monosaccharides. Disaccharides and trisaccharides are also anhydride forms which contain, respectively, two and three monosaccharide units and are also hydrolysed to monosaccharides. These are called **oligosaccharides** (Greek, *oligos*, few). They include disaccharides, trisaccharides, tetrasaccharides, etc., containing a few monosaccharide units which form the molecule of a polysaccharide. Finally, the monosaccharides themselves, which constitute the basic structural units of oligosaccharides (disaccharides, trisaccharides, etc.) and polysaccharides, also occur in small amounts in the free state in plants. The most widespread monosaccharides are pentoses, $C_5H_{10}O_5$, and hexoses, $C_6H_{12}O_6$. Heptoses, octoses, and other higher monosaccharides are also known to exist.

A. Monosaccharides

(a) *Structure of Monosaccharides*

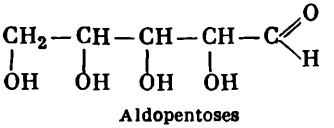
All pentoses can be reduced with hydriodic acid into secondary normal amyl iodide (pentyl), $CH_3CH_2CH_2CHICH_3$, and hexoses, into secondary normal hexyl iodide, $CH_3CH_2CH_2CH_2CHICH_3$, from which it is seen that pentoses and hexoses have an unbranched

* They were at one time referred to as "*hydrates of carbon*".—*Tr.*

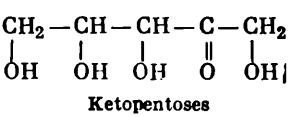
chain, the former consisting of five, and the latter of six carbon atoms. According to analytical data and molecular weight, all pentoses are represented by the formula $C_5H_{10}O_5$, and hexoses have the formula $C_6H_{12}O_6$. As a result of the acetylation with acetic anhydride or acetyl chloride, pentoses acquire four acetyl residues, i.e., they form an ester. Hence, they have four hydroxyls. The same reaction has established the presence of five hydroxyls in hexoses (A. A. Kolly, 1869). The addition of hydrocyanic acid, the reaction with hydroxylamine leading to an oxime and the oxidation with silver oxide or Fehling's solution, all these reactions show that one of the five carbon atoms in most pentoses is an aldehydic carbon. The first two reactions establish the presence of one carbonyl group in all hexoses. But some hexoses (glucose, mannose, galactose, etc.) have an aldehyde group, which is oxidized by Fehling's solution or an ammoniacal solution of silver oxide to a carboxyl group, while others (fructose, sorbose) and also ribulose (a pentose) contain a ketone group, which is oxidized neither by Fehling's solution nor by an ammoniacal solution of silver oxide but which adds hydrocyanic acid with the formation of a side branch, in contrast to aldehydic sugars, which when reacted with hydrocyanic acid lengthens the skeleton to form an unbranched, normal structure.

Aldehydic hexoses are referred to as **aldohexoses**, and ketonic hexoses, as **ketohexoses**. It is easy to establish that in natural ketohexoses the ketonic group occupies the second position since it is precisely in this position that the addition of hydrocyanic acid builds up a side branch in the carbon chain. All these facts point to the following structure for monoses (or monosaccharides):

Pentoses

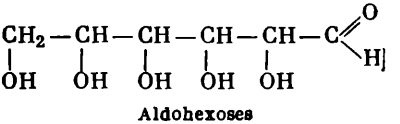


Aldopentoses

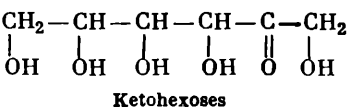


Ketopentoses

Hexoses



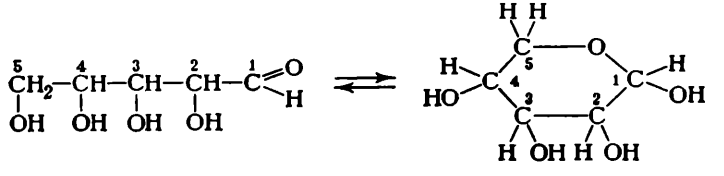
Aldohexoses

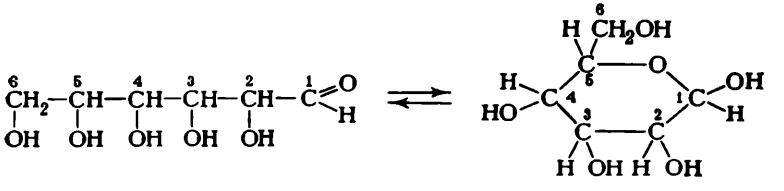


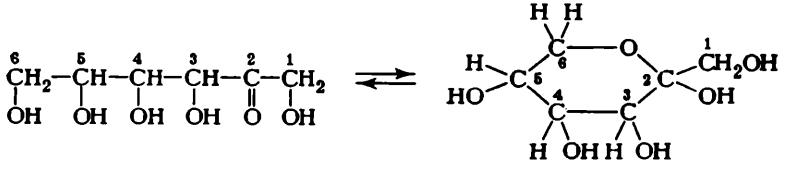
Ketohexoses

Indeed, each of the hydroxyl groups in these compounds appear to be linked to one carbon atom; two hydroxyl groups cannot be held by one carbon atom (Erlenmeyer's rule), and when the elements of water are eliminated, a carbonyl group is formed.

Thus, it would seem that the structure of monoses is easy to establish (E. Fischer). The task, however, is complicated by tautomerism, namely, by the **exo-ring tautomerism** which is characteristic of γ- and δ-hydroxycarbonyl compounds. This kind of tautomerism, which is also called **ring-chain tautomerism**, may be expressed by the following schemes:







Arguments in favour of the cyclic structure of monosaccharides had been known before the investigations carried out by Emil Fischer, and the first formulas suggested for monosaccharides were cyclic formulas which differed from those given above in that the carbonyl group was believed to interact not with a δ-hydroxyl group but with an α-hydroxyl group (A. A. Kolly) or with a γ-hydroxyl group (Tollens), and the ring was accordingly written as a three- or five-membered and not as a six-membered ring. In fact, as we shall see later, γ-closure occurs in monosaccharides too.

Emil Fischer assigned an open-chain structure to monosaccharides, having come to the conclusion that they give almost all the reactions

typical of carbonyl compounds. What arguments forced the chemists to return to the ring structure for monoses?

When alkylated with methyl iodide or dimethyl sulphate in alkaline medium pentoses acquire four and hexoses, five methyl groups, which is in keeping with the number of hydroxyl groups established by acetylation. Tetramethylpentoses and pentamethylhexoses, however, lose their ability to take part in aldehydic (or ketonic) reactions. Besides, one of these methyl groups differs sharply from the others in properties and, in general, from the alkoxy groups of ethers in chemical behaviour: whereas ethers are not hydrolysed in alkaline or acid solutions, this special methyl group, though being stable towards bases, is instantly hydrolysed with dilute acids, following which the monosaccharide, which still carries the other methyl groups, regains the properties of aldehydes (or ketones).

Recall that there are three principal types of alkoxy groups: ether alkoxyls hydrolysable neither by acids nor by bases; ester alkoxyls which are hydrolysed both by acids and bases; and acetal alkoxyls which are stable towards alkali and are hydrolysed by acids:

Ether methoxy group	*Ester methoxy group*	*Acetal methoxy group*
C_2H_5-O-CH	$CH_3-C(=O)-OCH_3$	$CH_3-C(H)(OCH_3)_2$

Thus, judging by its properties, the fourth (in pentoses) or the fifth (in hexoses) methyl group evidently enters into the composition of the **acetal group**.

There is one fact more. In acid medium monosaccharides are readily methylated by methanol, as a result of which they acquire only one methyl group, a group that has the above-mentioned properties of the acetal methyl group. Such derivatives are called **glycosides*** (a methylglycoside is formed in this particular case).

The properties of the carbonyl function again disappear in a methylglycoside. Besides, in acid medium the methyl group is readily eliminated on hydrolysis and the starting monosaccharide is reformed. Hence, it is the hydroxyl group carried previously by the

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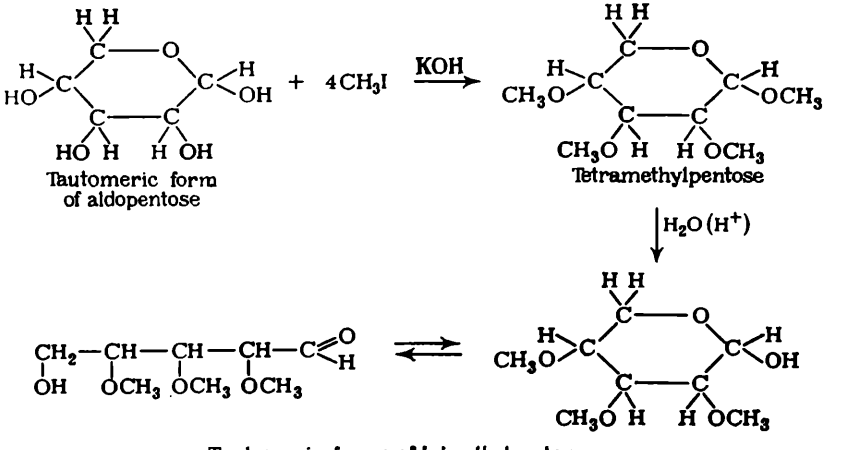
* The term **glycoside** is the generic name common to alkyl and other acetal derivatives of sugars; the term **glucoside** is used for those glycosides which contain glucose as the sugar, while glycoside refers to all compounds whatever the constituent sugar. The non-sugar portion of the molecule is called the **aglycone**.

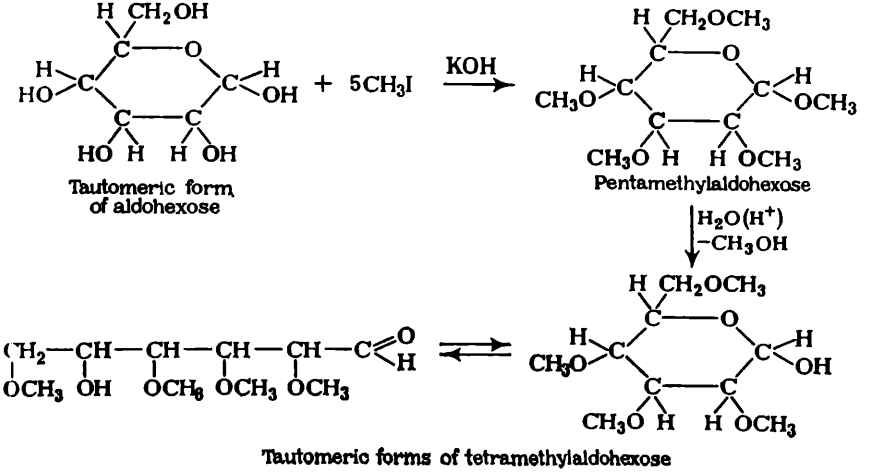
carbonyl carbon in a tautomeric cyclic form that undergoes alkylation in glycosides. All these facts are in agreement with the following methylation schemes:

1. *Methylation of an aldopentose*:



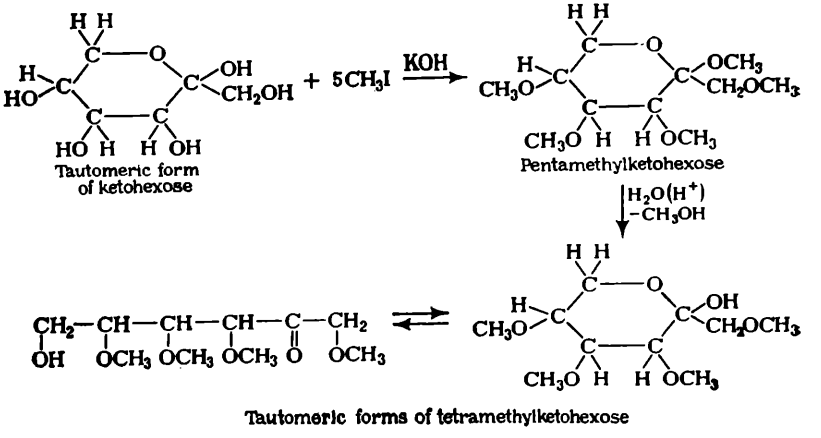
Tautomeric forms of trimethylpentose

2. *Methylation of an aldohexose*:

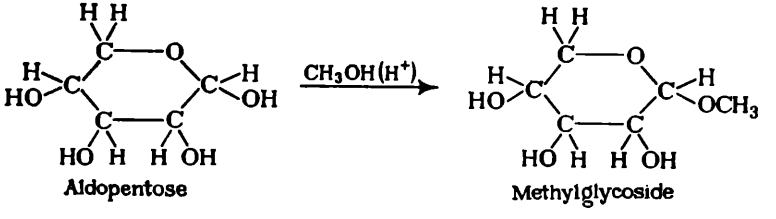


Tautomeric forms of tetramethylaldohexose

3. *Methylation of an ketohexose*:



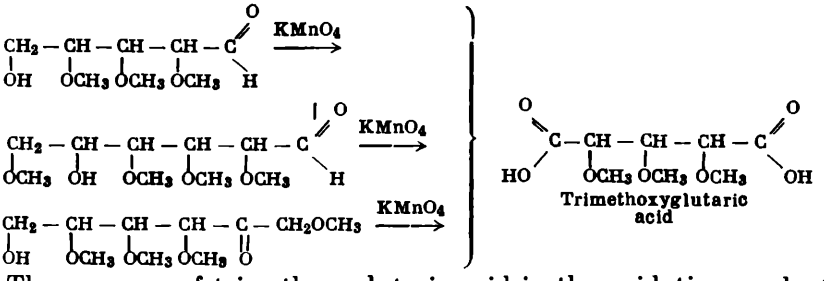
4. *The action of methanol*:



An especially clear-cut argument in favour of the peculiar properties of a single hydroxyl is the absence of an aldehydic (or ketonic) reaction during the displacement of the glycoside hydroxyl by a methyl group and its appearance upon removal of the methyl group by hydrolysis. The **glycoside hydroxyl** is the hydroxyl linked (previously) to the carbonyl carbon.

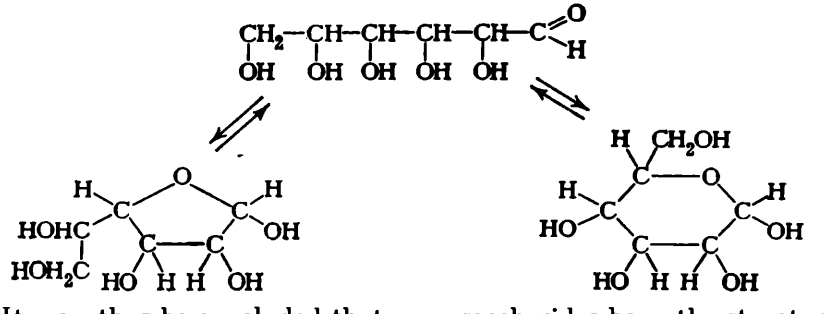
It remains to find out whether the ring in the cyclic form is six- or five-membered, as was assumed by Tollens, or else a different one. An answer to this question is provided by the oxidation of the methylation products of monosaccharides to dicarboxylic acids. Let us return to the open-chain tautomeric forms of methylated monoses given in schemes 1-3 and write down their oxidation reactions effected by permanganate. The oxidation is directed to the unmethylated hydroxyl and carbonyl groups since ethers are more stable towards

oxidation:



The presence of trimethoxyglutaric acid in the oxidation products clearly proves the δ-closure (a six-membered ring). In the case of γ-closure dimethoxysuccinic acid would be obtained and no trimethoxyglutaric acid would be present.

The use of these methods has provided a proof of the existence of three tautomeric forms of sugars—acyclic polyhydroxyaldehydes (*al*-forms), cyclic forms with a six-membered ring (pyranoses), and compounds with a five-membered ring (furanoses)*. These three forms are in a tautomeric equilibrium in solution, the pyranose form predominating. For aldohexoses this equilibrium may be depicted as follows:



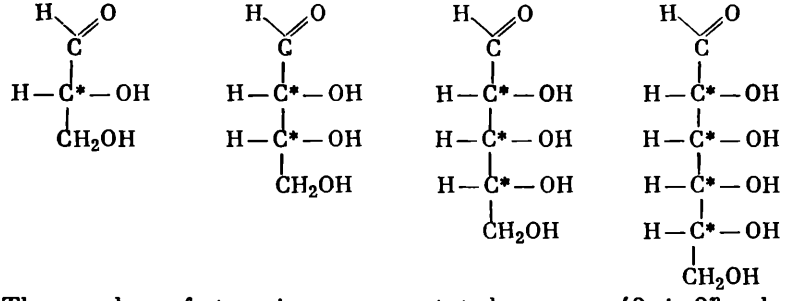
It may thus be concluded that monosaccharides have the structure of cyclic six-membered and five-membered hemi-acetals, this structure being tautomeric with the structure of hydroxyaldehydes or hydroxyketones. Tautomeric equilibrium systems, however, exist only in the liquid state (so-called **allelotropic mixtures** which are similar to mixtures formed by acetoacetic ester), or in solutions but not in crystals. The monosaccharides are solid crystalline compounds. Which of the tautomeric forms belongs to them in the crystalline state?

An answer to this question is given by stereochemistry which shows them to have a cyclic structure. An open-chain carbonyl form appears only in solution.

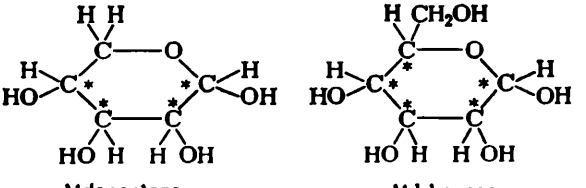
* These names are derived (Haworth) from the names of the heterocyclic compounds: pyran (six-membered) and furan (five-membered).

XV. Stereochemistry of Monosaccharides. Optical Isomerism II

Following E. Fischer, we shall first consider the stereochemistry of open-chain tautomeric forms of the monosaccharides. By considering this important example, it is necessary to ascertain the methods of establishing the configurations of monosaccharides by purely chemical means. In the series of compounds—from glyceraldehyde to an aldohexose (glucose)—the number of asymmetric atoms (marked with an asterisk) increases by one unit from member to member:



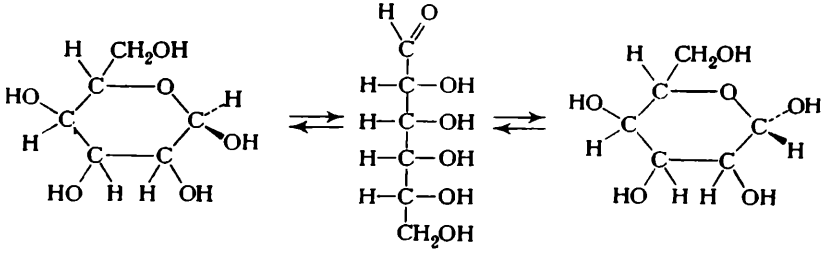
The number of stereoisomers, as stated on page 43, is 2^n, where n is the number of asymmetric carbon atoms. Racemates are ignored since they present no independent configurations. Thus, for glyceraldehyde the number of stereoisomers is 2 (the antipodes D- and L-glyceraldehyde); for aldotetroses there are 4 stereoisomers (two pairs of antipodes, each of them being diastereomeric to the antipodes of the second pair); for aldopentose the number of stereoisomers is 8 (four pairs of antipodes, each being diastereomeric with respect to the remaining six); for aldohexoses we have 16 stereoisomers (eight pairs of antipodes). Such must be the number of stereoisomers for the open-chain structures of the sugars. In actual fact, however, aldopentoses are known to have 16 and aldohexoses 32 stereoisomers (8 and 16 pairs of antipodes, respectively). Hence, the open-chain structures do not take account of the presence of one more asymmetric carbon atom in aldopentoses and aldohexoses. The cyclic forms have four asymmetric carbon atoms in aldopentoses and five in aldohexoses, which is in full harmony with the actual facts:



Aldopentose Aldohexose

In the solid state all 16 aldopentoses and 32 aldohexoses are quite stable. But once any of them is dissolved, say, in water, racemization begins around one of the carbon atoms, which can be traced quantitatively by placing the solution into the polarimeter tube. The rotation of the plane of polarization of the ray slowly changes (**mutarotation**) until a constant value is reached. This signifies the attainment of an equilibrium between two diastereomeric forms of the monosaccharide, which differ from each other only in the configuration of the first (previously, carbonyl) carbon atom, the other configurations remaining unaltered. (The amount of the open-chain form is negligibly small.)

The cause of mutarotation is quite clear: this phenomenon is associated with the tautomerization in solution and is expressed, for example, for an aldohexose, by the following scheme (in the perspective representation of cyclic forms only the arrangement around the first carbon atom is indicated, and the aldehyde form is given only in the structural and not the configurational formula):

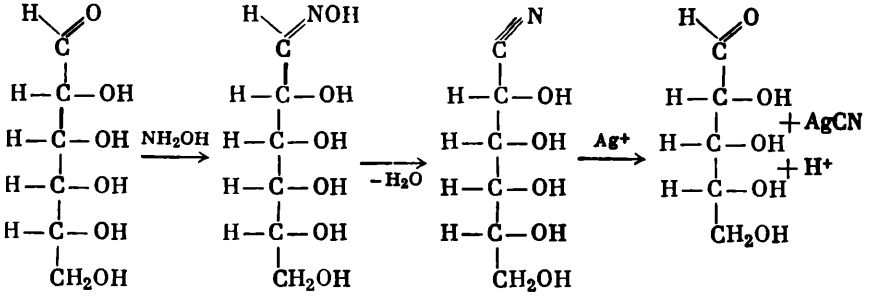


The diastereomers of sugars, which differ only in the configuration of the former carbonyl carbon, are designated as the α- and β-forms of the sugar. Just like any other diastereomers, they differ in properties, say, solubility, owing to which they can be separated from each other since the rate of interconversion of diastereomers is not too great.

To find out what configurations correspond to the α- and β-forms, it is necessary to solve the more fundamental problem, that of elucidating the configurations of the other asymmetric carbons that are stable in solutions.

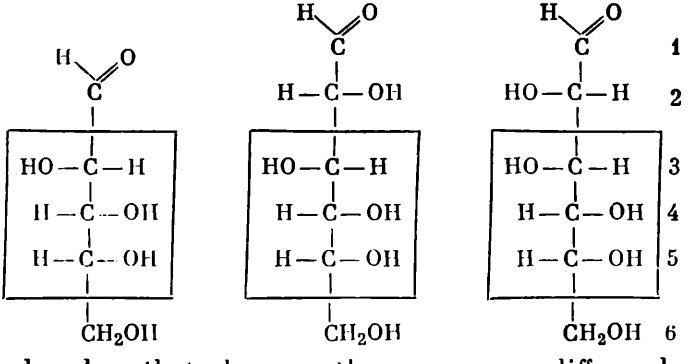
Let us recall that a number of compounds shown on page 103 are related to one another by the possibility of interconversion. Starting with an aldohexose it is possible to prepare, via an oxime, by elimination of water, the nitrile of aldopentonic acid which is then acted on by a silver salt to split off hydrocyanic acid and produce an

aldopentose:



It is obvious that this reaction makes it possible to establish the stereochemical similarity or differences between the aldohexoses, on the one hand, and between the aldopentoses, on the other.

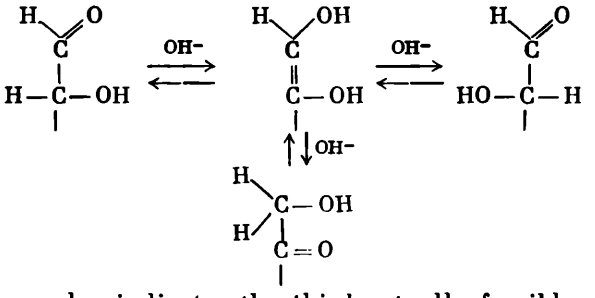
The fact that (+)-glucose (grape sugar) and (+)-mannose (and only this pair) give (+)-arabinose in such a transformation establishes the stereochemical similarity of these three monosaccharides in the region enclosed in squares in the formulas that follow (the formulas given are not stereochemical):



It is also clear that glucose and mannose may differ only in the configuration about the carbon atom (carbon-2) adjacent to the aldehyde group. Such a pair of sugars are known as **epimers***. Since in alkaline medium the monosaccharides are capable of keto-enol tautomerism, the enol form (more precisely, the enediol form) having a double bond between carbon-1 and carbon-2, the asymmetry of the second carbon atom in this form is lost, and in the reverse tautomerization of the enediol to an aldehyde either the left- or the right-hand configuration of carbon-2 may be formed. Hence, in alkaline solution the epimers are interconvertible (mannose and glucose are really

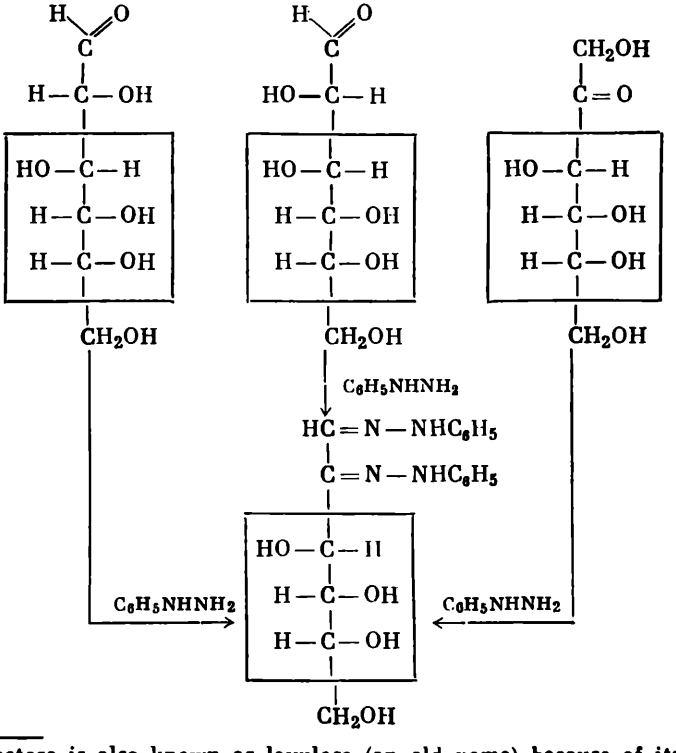
* In the carbohydrate literature, two sugars which differ only in the configuration at any one carbon atom are said to be epimeric. For example, glucose and galactose are epimers because they differ only in the configuration at C-4.

epimers):



The scheme also indicates the third actually feasible possibility of tautomerization of the enediol of glucose and mannose into a ketose. Experiment shows that (—)-fructose* is formed in this process. Thus, the interconversion of (+)-glucose, (+)-mannose and (—)-fructose takes place in alkaline medium via the enediol form up to the attainment of equilibrium. This again proves that the configurations about carbon atoms 3, 4, and 5 are the same in these three monosaccharides.

An additional proof is the identity of the osazones (page 104) of all

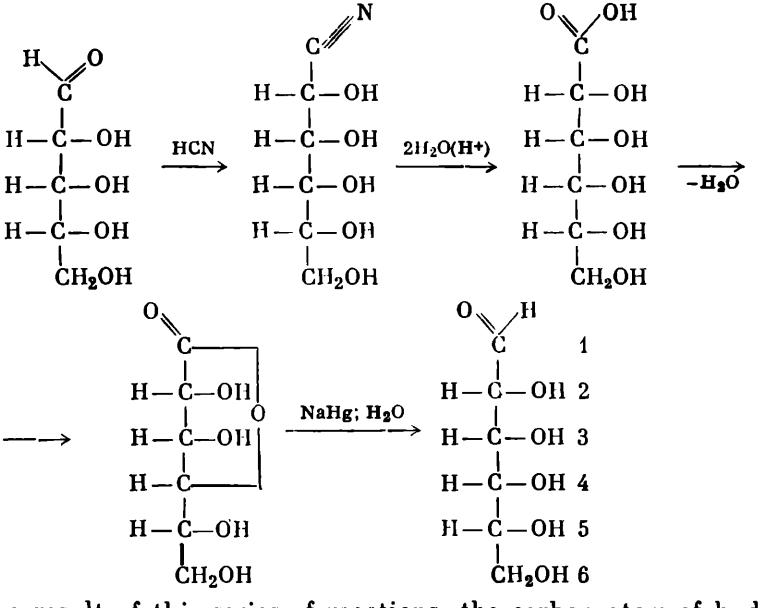


* Fructose is also known as levulose (an old name) because of its levorotation.

the three monosaccharides: mannose, glucose, and fructose (the formulas given are not stereochemical).

It is clear that among the 16 stereoisomers of aldohexoses (neglecting the α- and β-forms) there are eight pairs of epimers that have such relationships, and each such pair has a corresponding stereochemically related ketohexose. How could the configuration of each of the eight aldopentoses and each of the 16 aldohexoses be elucidated? Apart from the elucidation of the configurational relation between the higher and the lower monosaccharides by the degradation via an oxime and a nitrile, we have also mentioned the reverse, synthetic pathway for establishing such a relation.

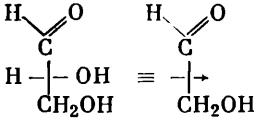
Let us now make use of this route for the conversion of an aldopentose into an aldohexose:



As a result of this series of reactions, the carbon atom of hydrocyanic acid has become the aldehyde carbon of an aldohexose and the aldehyde carbon of an aldopentose has become a carrier of a new grouping, H—C—OH, and turned into an asymmetric carbon atom. Taking into account the inevitable formation of both possible groupings (the left- and the right-hand) about the newly formed asymmetric carbon atom, we come to the conclusion that in such a synthesis an aldopentose yields two epimeric aldohexoses (since the newly formed asymmetric carbon atom with the H—C—OH grouping is the second carbon atom of the aldohexose).

Let us now turn to the systematic building of all possible tetroses, pentoses, and hexoses by this method **(the cyanohydrin method)**

starting with one of the enantiomers of glyceraldehyde. We choose D-(+)-glyceraldehyde as the starting material. For the sake of brevity we shall denote the grouping H—C—OH by an arrow pointing from H to OH in stereochemical formulas—Fischer projections (see Volume I). Then the formula of (+)-glyceraldehyde will be as follows:

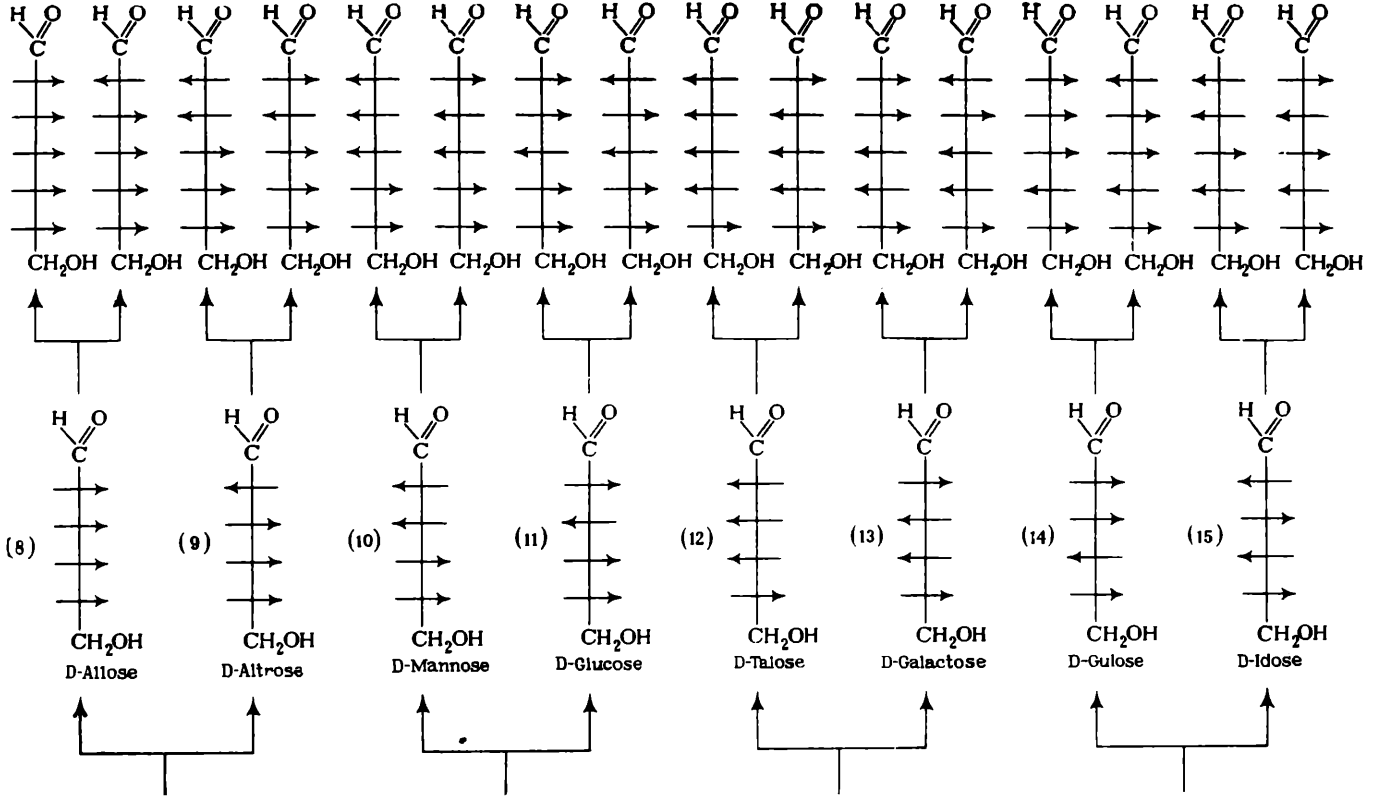


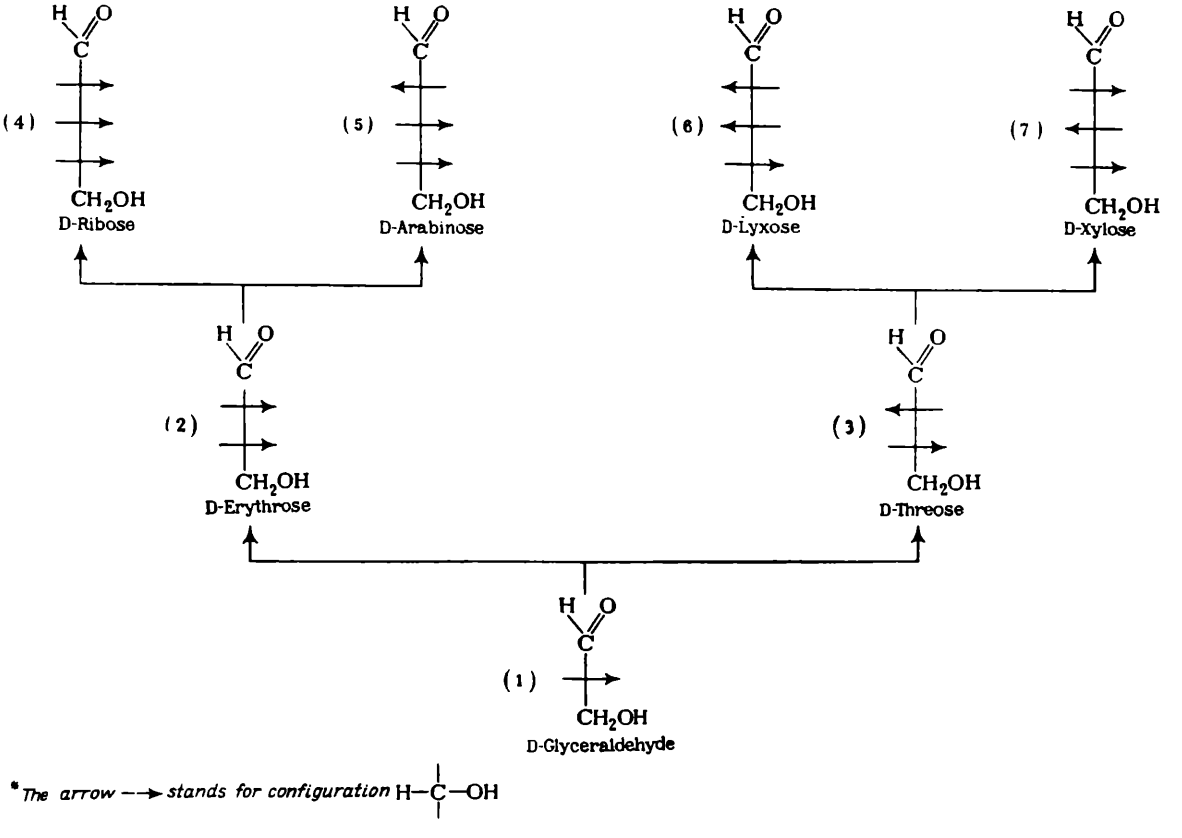
Note that for each new H—C—OH link to be built up by means of the cyanohydrin method there are two possibilities, i.e., → and ←. In a table of the stereoisomers obtained in this way we shall place first (on the left) that stereoisomer in which the newly written arrow lies in the same direction as the previous one, and next to it (on the right) the one, in which the arrow is in the opposite direction with respect to the previous one. Let us now write out the entire series of aldoses produced in this way from D-(+)-glyceraldehyde (Table 4.8). The same operation could be performed with L-(—)-glyceraldehyde, in which case we would obtain the mirror image of the same scheme and to each monosaccharide in it there would correspond its antipode. The antipodes are omitted in Table 4.8. It contains only the stereochemical formulas of the aldoses of the D-series. It is clear that the letter D is the configurational family sign indicating only the relationship to D-glyceraldehyde. It bears no relation to the dextro or levo rotation of the plane of polarization which is indicated by the signs (+) and (—). Specifically, the letter D signifies that the configuration about carbon atom 2 (numbering is started with the terminal aldehyde group, its carbon being 1; carbon 5 in the case of hexoses) of a monosaccharide prefixed with D is the same as the configuration about the equivalent carbons of D-glyceraldehyde.

The building up of the first additional CHOH group in D-glyceraldehyde results in the formation of two aldotetroses, D-erythrose and D-threose. When the aldehyde and primary alcohol groups are oxidized to carboxyl groups, erythrose (2) is transformed into meso-tartaric acid 2′ and threose (3) into L-(—)-tartaric acid 3′ (not shown in Table 4.8; see page 46). The configuration of the aldotetrose is thus established.

Let us now take up the task of establishing the configurations of three related monosaccharides (which are somewhat familiar to us) — arabinose, glucose, and mannose, since this is quite enough in order to understand the principle of configuration assignment according to the chemical (and optical) properties of a compound (see Tables 4.8 and 4.9). We know four D- and four L-aldopentoses: ribose, arabinose, lyxose, and xylose (4, 5, 6, 7). When oxidized (see Table 4.9) to dicarboxylic acids (4′, 5′, 6′, 7′) ribose and xylose

TABLE 4.8. The Building up of the D-Series of Aldoses from D-Glyceraldehyde*



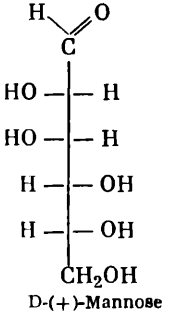


*The arrow ⟶ stands for configuration H—C—OH

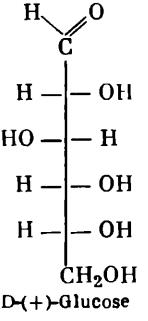
form optically inactive (*meso*) acids (4′ and 7′), whereas arabinose and lyxose give optically active acids (5′ and 6′). This can be established if we cut the formulas just in half (through carbon-3 in this particular case) by the plane of symmetry (a mirror), in which case we shall find that both halves of the molecule are mirror images of each other, which points to the optical inactivity due to the internal compensation of the *meso*-form. Hence, arabinose may have the configuration (5) or (6) and not (4) and (7). In order to choose between (5) and (6) we need additional experimental facts. Some of them are known. When arabinose is stepped up, glucose (11) and mannose (10) are formed. When oxidized to dicarboxylic acids—saccharic (glucaric) and mannosaccharic (mannaric) acids, they give optically active acids. It is easy to see that this fact rules out the configuration (6) for arabinose because the aldohexose (13) derived from the aldopentose (6) yields on oxidation a *meso*-form—acid (13′). Therefore, the configuration (5) is chosen for arabinose, and the configurations (10) and (11) for mannose and glucose, respectively. The problem of the configuration of ribose is solved in passing: ribose and arabinose give the same osazone, i.e., they differ only in the configuration of the second carbon atom (the first is the aldehyde carbon). Hence, ribose has the configuration (4).

The facts given above do not, however, allow us to decide which of the two formulas belongs to mannose and which to glucose. New facts are needed. They are as follows. If these two aldohexoses are built up to give aldoheptoses, then mannose forms two aldoheptoses, each of which on oxidation yields two optically active dicarboxylic acids. When glucose is stepped up, it gives two aldoheptoses, each of which when oxidized to dicarboxylic acids forms one optically active form and one inactive (*meso*) form. This leads us to choose the configuration (11) for glucose and (10) for mannose. The configurations of other pentoses and hexoses are established in a similar way (by conversion to the *meso*-form).

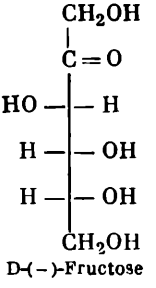
Once the configurations of glucose and mannose are established, we can arrive at the configuration of fructose. Below are written the configurations of these hexoses in the tautomeric aldo form:



D-(+)-Mannose



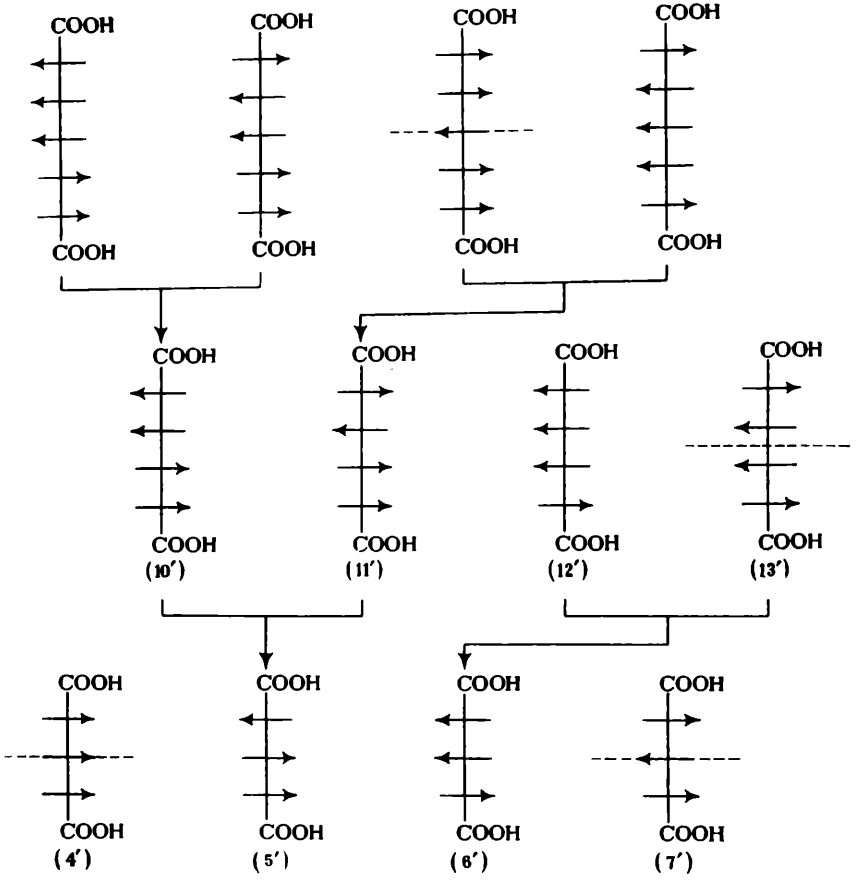
D-(+)-Glucose



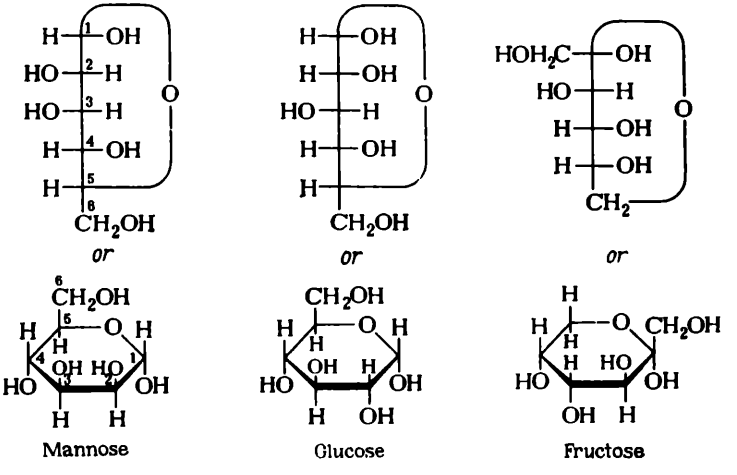
D-(−)-Fructose

TABLE 4.9. The Oxidation of D-Aldopentoses, D-Aldohexoses, and D-Aldoheptoses to Dibasic Acids (Optically Active or Inactive Due to Internal Compensation)

(the dashed line indicates the projection of the plane of symmetry; 4′, 7′ and 13′ are *meso*-forms)

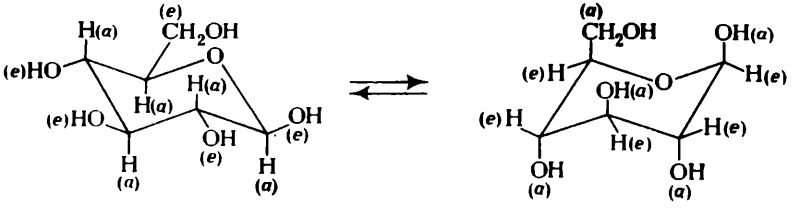


The cyclic tautomeric forms of these three sugars are represented in Fischer projections and in Haworth perspective formulas (in these formulas the plane of a six-membered ring should be regarded as lying perpendicular to the plane of the drawing and the thickened sides of the hexagon imply that these sides are nearer to the eye than the others). The asymmetric carbon atoms are omitted in Haworth formulas, just as in Fischer projections.



It should be kept in mind that the Haworth perspective formulas do not correspond to the true geometric form of the monosaccharide molecule either. The point is that the pyranose ring*, just as the cyclohexane ring, is not flat but exists in a chair or a boat conformation, the chair form being, as a rule, energetically more favourable (page 211).

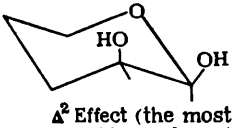
Owing to the presence in the pyranose ring of an oxygen atom, which changes the ring symmetry, it may have a larger number of conformations than there may exist for cyclohexane (see page 211). For example, two different chair conformations are possible for glucose:



* The pyranose ring is six-membered and consists of five carbon atoms and one oxygen atom.

The preferred conformation, in which the given monosaccharide actually exists, is determined, just as in the case of cyclohexane derivatives, by the ratio of the sizes and the number of the substituents which are in the equatorial (*e*) and axial (*a*) positions.

The reactivity of the substituents is different, depending on whether they are in the equatorial or in the axial position. Determination of the conformation of a monosaccharide **(conformational analysis)** is therefore of great importance in the chemistry of carbohydrates. Approximate determination of the conformation can be made through the estimation of the most energetically favourable position of the substituents in the competing conformations: the molecule tends to assume such a conformation in which the maximum number of more bulky substituents are in the equatorial position (glucose therefore actually exists only in the conformation written on the left). We can predict the most probable conformation of a molecule if we know, from experimental data, the values of instability number of each substituent and take into account the presence of certain unfavourable conformational factors, say, the so-called Δ^2-effect (the disposition of the glycoside hydroxyl between the cyclic oxygen and the hydroxyl at carbon-2, and hence the approach of the three oxygen atoms).



Δ^2 Effect (the most unfavourable conformation)

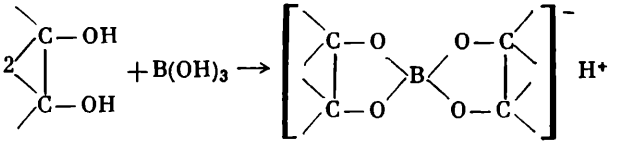
For experimental determination of the conformation, advantage was made of the fact that sugars, like glycerol, have more acidic hydroxyl groups than those in alcohols, and therefore give alkoxides **(saccharates)** with ions of heavy metals.

Such alkoxides of copper have a cyclic structure and are formed only when two neighbouring hydroxyls are in a single plane or are close to such an arrangement. If the properties of a sugar in solution are observed, say, its optical rotation, the moment of formation of such a copper derivative can be fixed. By controlling the change of the optical rotation of individual monosaccharides on addition of copper salts to them, it has become possible to establish in which cases copper saccharates are formed, i.e., to arrive at a conclusion as to the relative spatial arrangement of the neighbouring hydroxyls in these monosaccharides and, hence, to establish the conformations of all monosaccharides (R. F. Reeves).

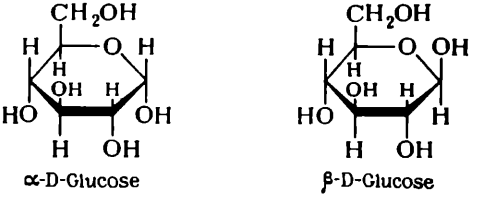
At present, the conformations of monosaccharides are deduced on the basis of a study of their nuclear-magnetic-resonance (NMR)

spectra*. The point is that the chemical shift and, especially, the spin-spin interactions for protons occupying the equatorial and axial positions are different. With the appropriate parameters of the protons of the C—H bonds known, this allows one to locate the position of these bonds in space, i.e., the conformation of the molecule.

In all the formulas given above the configuration of the glycoside carbon atom is chosen arbitrarily since it has not been conclusively determined. What remains to be determined is the configuration of this glycoside carbon atom in α- and β-monoses. For glucose, this problem is solved on the basis of its reaction with boric acid. Glycols and polyhydric alcohols, whose hydroxyl groups can freely turn to one side (non-rigid structures such as ethylene glycol and glycerol) or are pointed in one direction (in rigid structures such as small rings), form strong acids with boric acid:



Their acid reaction can be detected with the aid of indicators. β-Glucose does not enter into reaction with boric acid, which means that it has no hydroxyls turned to one side. α-Glucose gives this reaction. This signifies that the glucoside hydroxyl and the one adjacent to it (i.e., the hydroxyls in positions 1 and 2) are arranged on one side of the ring. Thus, α- and β-glucoses have the following configurations:



α-D-Glucose β-D-Glucose

These two stereoisomers of glucose, which differ only in the configuration of carbon-1 (for aldoses; of carbon-2 for ketoses), are known as **anomers** (the α- and β-anomers). The above formulas represent the anomers of D-glucose.

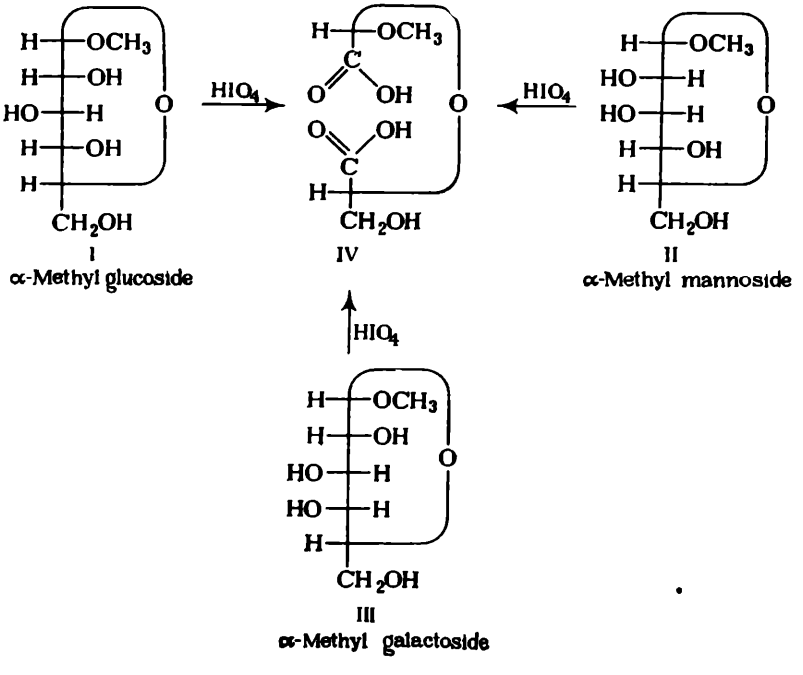
This method of assignment of a monosaccharide to the α- or β-series is however applicable only in those cases if there is no other pair of hydroxyl groups on one side of the plane of the ring (in the *cis*-position). At present, this purpose is most frequently achieved through the use of nuclear-magnetic-resonance (NMR) spectroscopy (page 292).

* For nuclear-magnetic-resonance (NMR) spectra, see Sec. XXV (B).

The chemical shift for the protons of the glycoside hydroxyl of α- and β-monosaccharides varies markedly: for the α-anomers (the D-series) the shift is only 4.8τ, while for the β-anomers it varies within the range of 5.2-5.45τ.

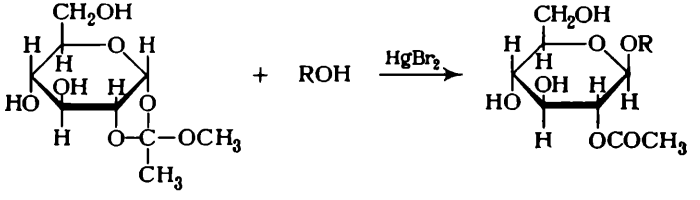
The NMR method is employed even for the determination of the equilibrium between α- and β-anomers in solution.

In general, the α-configuration of the aldoses is one in which the configuration of the first carbon atom is the same as that of the parent compound—glyceraldehyde (or, which amounts to the same thing, as the configuration of carbon-5 in hexoses). C. S. Hudson established the identity of the configurations of carbon-1 in α-glucose, α-mannose and α-galactose by converting them into the corresponding methylglycosides with subsequent oxidation of the latter with periodic acid (see Volume I, page 340). As a result, he obtained the same compound (IV):



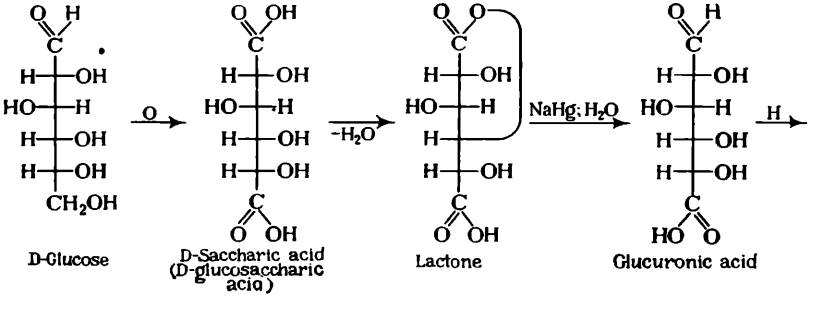
Since in this oxidation reaction the bonds with carbon-1 remains intact (meaning that neither Walden inversion nor racemization is possible), the fact that the resulting compound is the same acid (IV) proves the identity of the configurations of carbon-1 in all the three monosaccharides.

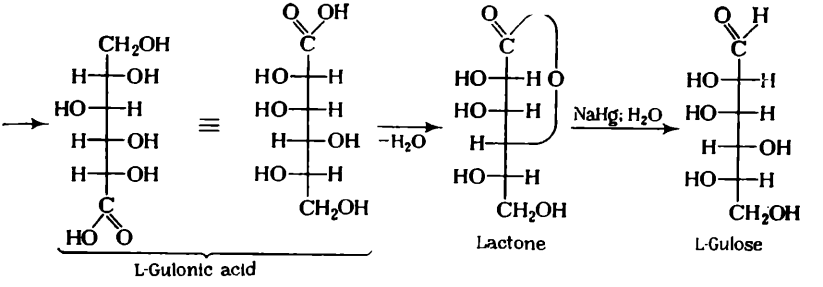
An important method of synthesizing glycosides, which gives a definite anomer, has been worked out by N. K. Kochetkov and A. F. Bochkov. The method consists in the interaction between the orthoesters of sugars (orthoacetates or orthobenzoates of mono-, di-, etc., saccharides) with hydroxylic compounds in the presence of mercuric bromide as a catalyst. For instance, the reaction of glucose is as follows:



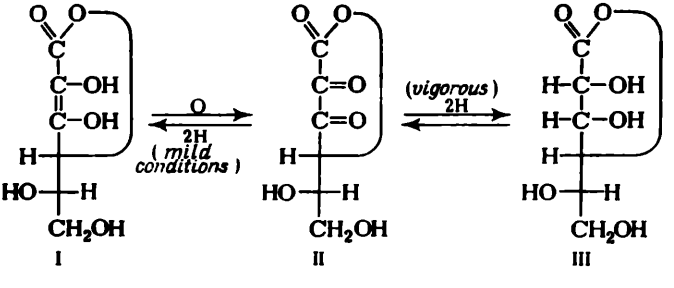
The reaction is applicable to the various hydroxyl-containing compounds: simple and complex alcohols (for example, steroid alcohols), sugars to be stepped up by a new monosaccharide unit (synthesis of di-, tri- and other saccharides), phenols (synthesis of aryl glycosides), etc. In this way, glycosides can be synthesized from any sugars having the pyranose and furanose structures. The method is quite universal. It has definite advantages over the only known general method of glycoside synthesis (glycosylation) developed by Königs and Knorr (via acetohalogenoses) since it proceeds under very mild conditions and strictly stereospecifically, with the formation only of 1,2-*trans*-glycosides (in the case of glucose, β-glucosides are obtained).

Of interest are the methods of conversion of the monoses of the D-series into those of the L-series. As an illustration, we give the following example:





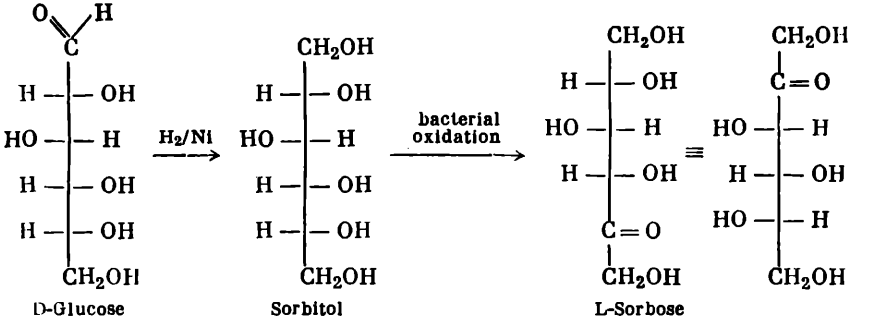
The above series of reactions which involve group transformations, thereby effecting the maneuver from the D- to L-series, is employed on an industrial scale for producing **vitamin C** or **ascorbic acid**, which plays such a vital role in the regulation of biological oxidation-reduction processes (aiding cellular respiration by acting as a hydrogen transporter) that man cannot exist without consuming vitamin C in his diet (the daily adult requirement is about 20 mg). It assists the body to withstand bacterial infection and toxins and is essential for the prevention of scurvy due to its antiscorbutic activity. A deficiency of vitamin C weakens the organism, increases its sensitivity to bacterial infection and toxins and may even cause scurvy if its content is too low. Ascorbic acid was the **first vitamin** isolated in the pure state in 1928 by A. Szent-Györgyi from a number of natural sources. Later it was synthesized from glucose. The structure of ascorbic acid (I) is the enediol structure of the lactone of α-ketogulonic acid (Haworth, Karrer, Hirst), which is deduced from its oxidation to diketogulonic acid (II) and conversion, on vigorous reduction, into lactone (III). The oxidation to the diketonic form II and the reverse reduction of II to the enediol form I



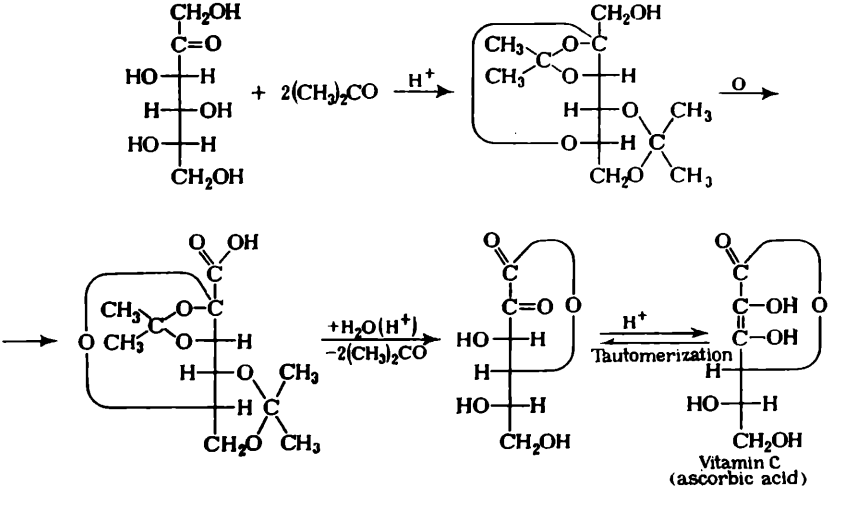
proceed exceedingly readily and contribute to some of the oxrdation-reduction reactions in the living cell.

The starting material used for the industrial synthesis of ascorbic acid is glucose which is reduced to sorbitol, the latter being sub-

jected to fermentation with *Acetobacter xylinum* to L-sorbose:

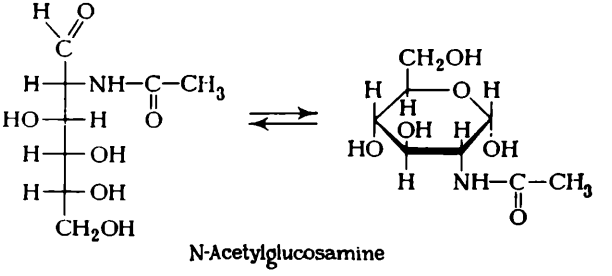


The L-sorbose obtained is converted by the action of acetone in acid solution into a ketal to protect the two secondary and one of the primary hydroxyl groups against oxidation. In a diacetonide, the sorboses oxidize the other primary alcoholic group to a carboxyl group, following which the acetone is removed by hydrolysis. Then the carboxyl esterifies the γ-hydroxyl group to give a lactone, after which the tautomerization into an enediol takes place:

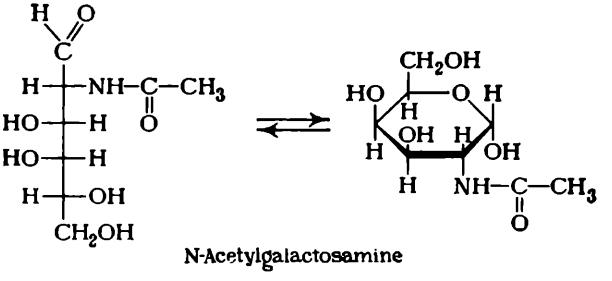


Apart from the above-mentioned monosaccharides of the D- and L-series, a large number of monosaccharides, in which one or more hydroxyl groups are replaced by other groupings, have been isolated from bacteria and plants and synthesized. The most important of these are **amino sugars** in which one of the hydroxyl groups is replaced by a primary amino group, more often by an acetylated one. 2-Amino sugars which contain an amino group at carbon-2, say,

glucosamine and galactosamine, enter into the composition of many polysaccharides: **chitin**, which forms the integument (exoskeletal structures) of crustaceans, insects and fungi; **heparin**, an anticoagulant which inhibits the clotting of blood in the human body; **chondroitins** which are the main principal constituent of cartilage and tendons; substances which determine the blood group, and others. Amino sugars are also contained in antibiotics.

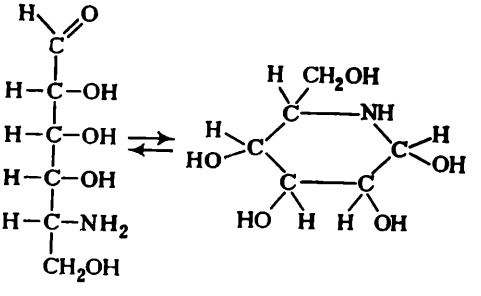


N-Acetylglucosamine



N-Acetylgalactosamine

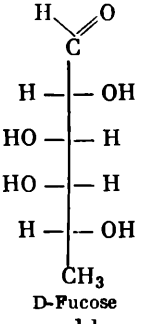
It is interesting that 5-amino sugars exist not only in the carbonyl form, but also in such cyclic forms in which the ring is closed not at an oxygen atom but at a nitrogen atom (so-called **piperidinoses**):



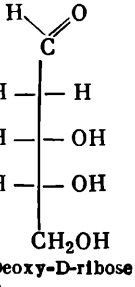
Piperidinoses lose water rather readily to form the derivatives of an aromatic heterocyclic compound — pyridine (see Volume III).

A number of monosaccharides are well known, in which one or more hydroxyl groups have been replaced by a hydrogen atom. They are

called **desoxy sugars** (or **deoxy sugars**). As examples may be cited 6-deoxygalactose, or **fucose**, which is a constituent of sea-weed polysaccharides, and **2-deoxy-D-ribose** which enters into the composition of deoxyribonucleic acids (DNA, see Volume IV):

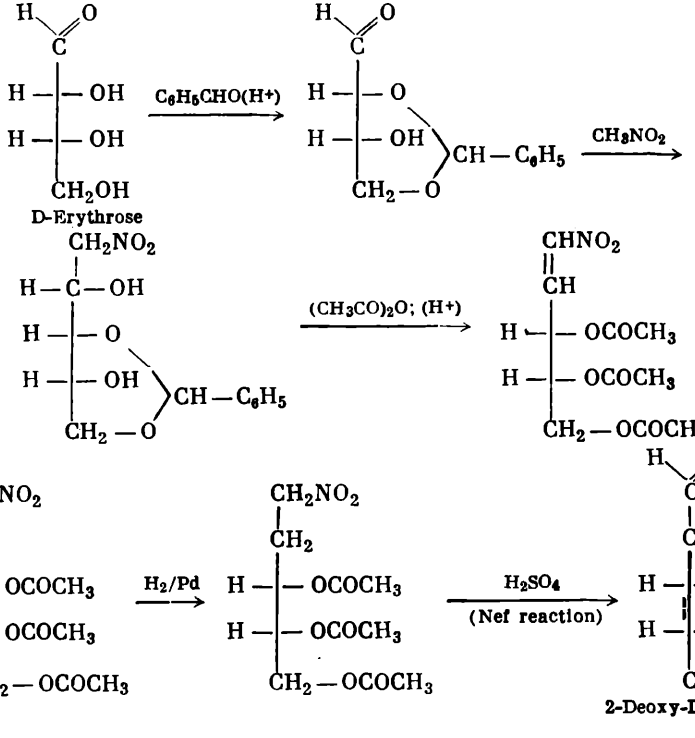


D-Fucose



2-Deoxy-D-ribose

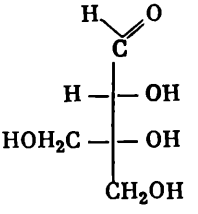
To prepare 2-deoxyaldoses, use is made, among other methods, of their synthesis from aldoses with a smaller number of carbon atoms by building up the chain through the condensation with nitromethane (the Henry reaction). An example is the synthesis of 2-deoxy-D-ribose from erythrose (the hydroxyl groups are first protected by acetal formation by means of benzaldehyde):



2-Deoxy-D-ribose

There also exist **thio sugars** in which the SH group has taken the place of the hydroxyl.

Sugars having not a straight but a branched chain of carbon atoms have been isolated from some algae (see-weeds) and antibiotics. An example is **apiose**



Apiose

XVI. Alcoholic Fermentation and Cellular Respiration

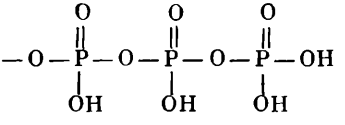
A number of monosaccharides (glucose, fructose, mannose, galactose) and also disaccharides (maltose, sucrose, lactose) undergo fermentation under the influence of living yeast cells, being converted into ethanol and carbon dioxide. Disaccharides are first hydrolysed. The summary equation for monoses is

$$C_6H_{12}O_6 \longrightarrow 2C_2H_5OH + 2CO_2$$

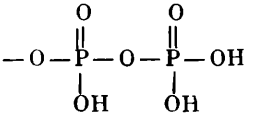
Yeast is known to be living unicellular organisms (fungi) which reproduce in the sugar medium; for its life to be sustained, the medium must contain ammonium salts (as a source of nitrogen for synthesis of its proteins), salts of phosphoric acid and some other mineral salts. Yeast can however be submitted to strong pressure, as a result of which its cell walls are disrupted and an "expressed yeast juice" is obtained, which no longer contains living cells (E. Buchner) or else it can be dried and extracted with water (A. N. Lebedev). The juice and extract thus obtained nevertheless possess strong fermentative power and is capable of exerting a catalytic action and causing the conversion of sugars into alcohol, just as living yeast cells. The cell-free yeast juice that ferments sugars has been called **zymase**. Zymase has been found to contain an entire complex of enzymes, many of which are also present in animal and plant cells, where they catalyse, during the cellular respiration, the same conversions of sugars (glucose and fructose) which take place at the first stage of the fermentation process. The names of these enzymes are given in the scheme on page 134. The structure of enzymes is discussed in Volume IV under "Enzymes".

The fermentation and breakdown processes occurring during the cellular respiration due to the air oxygen involve not the monoses themselves but their esters and phosphoric acid as well. The esterification of a monosaccharide by phosphoric acid in aqueous solution is accomplished by the action of adenosine triphosphate.

Adenosine triphosphate (abbreviated to ATP further in the text) plays a prominent part in biochemical and physiological processes. This compound will be treated in more detail in sections concerned with heterocyclic compounds and enzymes (see Volumes III and IV, respectively). At this point, it will suffice to note that ATP contains the grouping



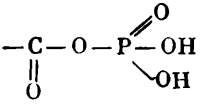
Supplying one phosphoric-acid residue to a monose, ATP convert it into an ester, monosophosphate, and is itself transformed in the process into **adenosine diphosphate** (ADP) containing the grouping



As can be seen even from this formula fragment, ADP is basically an ester of pyrophosphoric acid. Both ADP and, notably, ATP are very reactive compounds possessing the so-called **energy-rich phosphate bonds** (P—O—P); in phosphorylation reactions, i.e., in phosphate transfer, or migration, reactions, when these bonds are broken, a large quantity of energy is liberated. And, conversely, the formation of ATP from ADP requires the consumption of energy (8-10 kcal/mole) which is absorbed by its energy-rich molecule.

The first stage in the breakdown of glucose in the course of cellular respiration (these are multistage processes; see the scheme on page 134) is the phosphorylation of glucose (I), i.e., the formation of an ester of phosphoric acid (glucose-6-phosphate). The esterification takes place across the hydroxyl at carbon-6 of glucose by means of ATP in the presence of the enzyme glucokinase. The glucose-6-phosphate (II) formed changes under the influence of the enzyme isomerase to fructose-6-phosphate (III). (If fructose undergoes fermentation, then the phosphorylation results directly in the formation of 6-phosphate III.) Then the phosphate ester (III) is once again phosphorylated at the first hydroxyl group under the action of a new molecule of ATP (the enzyme is phosphofructokinase). The resulting fructo-

se-1,6-diphosphate* (IV-V) is cleaved by the action of the enzyme aldolase (a reverse aldol condensation) to give dihydroxyacetone phosphate (VI) and glyceraldehyde-3-phosphate (VII). These two triose phosphates are reversibly interconverted (VI $\rightleftharpoons$ VII) by the action of the corresponding isomerase (enzyme). Further transformation involves only phosphate (VII). The meaning of the subsequent conversion is that glyceraldehyde-3-phosphate is oxidized by a peculiar process**(the compounds VIIa and VIIb) to a derivative of the 3-phosphate ester of glyceric acid, namely, to a mixed anhydride of glyceric and phosphoric acids (VIII), which also has an energy-rich phosphate bond:



The exchange reaction between VIII and ADP once more regenerates ATP and the 3-phosphate of glyceric acid (IX) is produced. The action of the enzyme phosphoglyceromutase converts 3-phosphate (IX) into 2-phosphate (X) which then loses a water molecule and changes (by the action of the enzyme enolase) into the phosphate of the enolic form of pyruvic acid (XI). In this phosphate, the linkage between the phosphoric-acid residue and the enolic oxygen is also energy-rich. Therefore, when ADP reacts with phosphate (XI), it takes up the phosphoric-acid residue and is again phosphorylated to ATP, and the enolic form of pyruvic acid liberated is tautomerized into pyruvic acid (XII).

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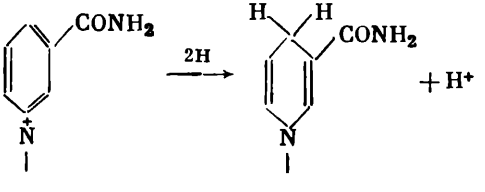
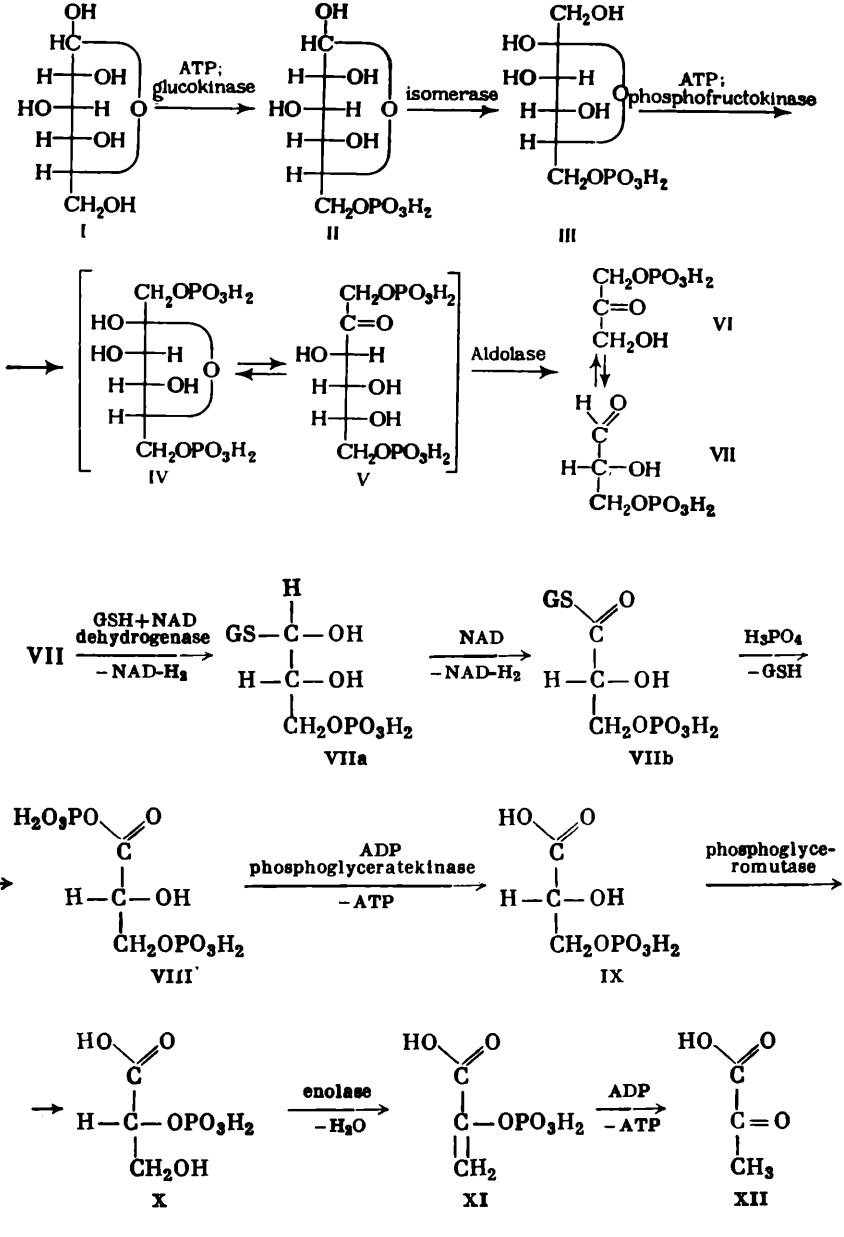
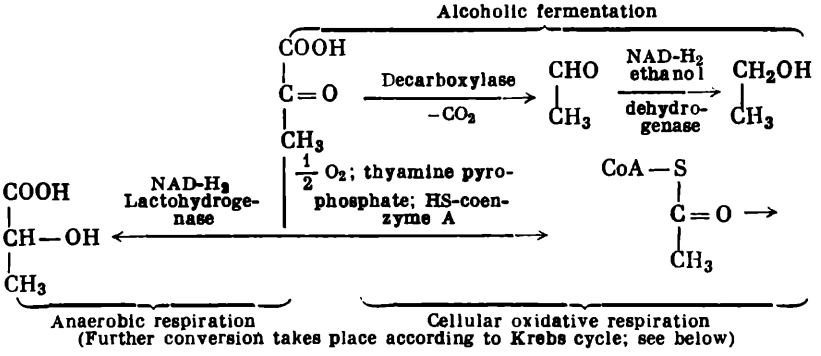
* Fructose-1,6-diphosphate is often called *the Harden-Young ester* after the investigators who isolated it from the fermentation products obtained by the action of the cell-free yeast juice, zymase, on a mixture of glucose and inorganic phosphate. — *Tr.*

** With the participation of glutathione GSH (see page 185) linked to the enzyme dehydrogenase and of nicotinamide-adenine dinucleotide (NAD); the former gives its mercapto group to ester VII and the latter acts as a hydrogen carrier. Accepting hydrogen, NAD is reduced to NAD-H_2, part of its molecule undergoing the following changes:





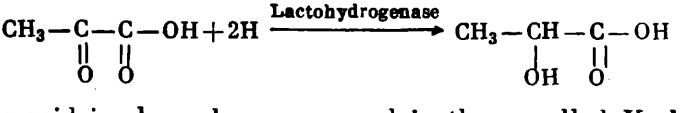
At this point the paths of alcoholic fermentation, anaerobic respiration and cellular oxidative respiration take different courses:



In alcoholic fermentation, the enzyme decarboxylase decarboxylates pyruvic acid to acetaldehyde, which is reduced to ethanol at the expense of the molecule of NAD-H_2* which has previously added on hydrogen upon transformation of VII to VIII. In anaerobic respiration, the same reducing agent, NAD-H_2, reduces pyruvic acid to lactic acid. On the pathway from glucose to lactic acid there is liberated about 50 kcal/mole, of which 16-20 kcal is consumed for the formation of 2 moles of ATP. In cellular respiration involving oxygen, pyruvic acid, being oxidized by the oxygen in the presence of thiamine pyrophosphate and coenzyme A (usually abbreviated to CoA—SH), is converted into acetyl coenzyme A, whose acetyl group is oxidized further to carbon dioxide and water by the reactions of the Krebs cycle.

XVII. The Dicarboxylic and Tricarboxylic Acid Cycle (Krebs Cycle or the Citric Acid Cycle)

The central role played by pyruvic acid in the breakdown, or degradation, of sugars is apparent from the scheme given above. In lactic fermentation, it also serves as a key compound, being formed according to the same scheme and then reduced to lactic acid:



Pyruvic acid is also a key compound in the so-called **Krebs cycle**, or the **citric acid cycle**, which is of enormous importance in the

* In newer terminology DPN (diphosphopyridine nucleotide) is replaced by NAD.—*Tr.*

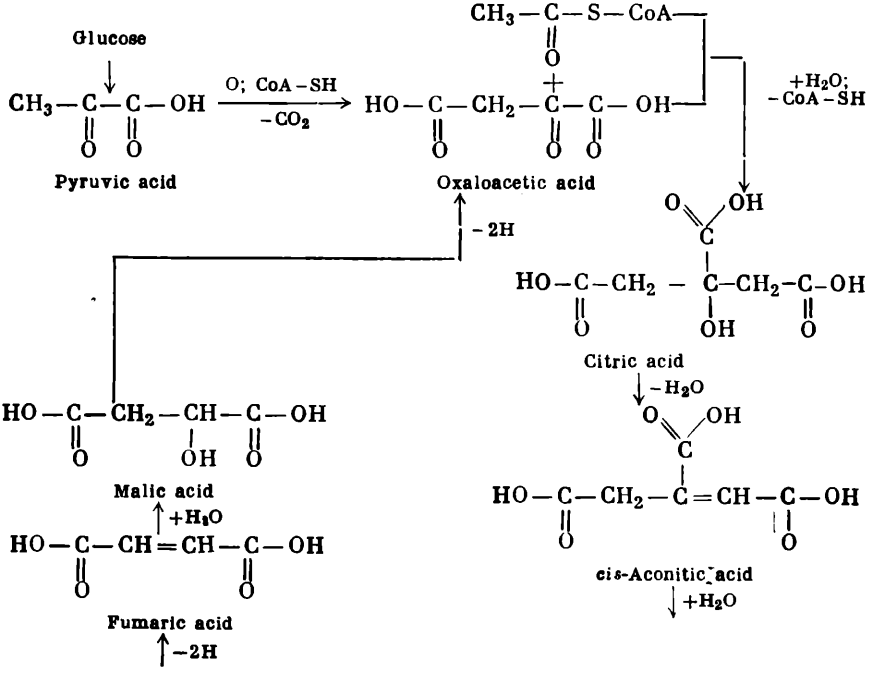
metabolism of plant and animal organisms. Biochemically important acids, such as citric, ketoglutaric, succinic, fumaric, and malic, are built up of the units of the Krebs cycle. The full cycle is a cycle of cellular respiration in animals and plants, which leads to the oxidation of 1 mole of pyruvic acid (which in its turn is formed from glucose) to 3 moles of carbon dioxide and 2 moles of water.

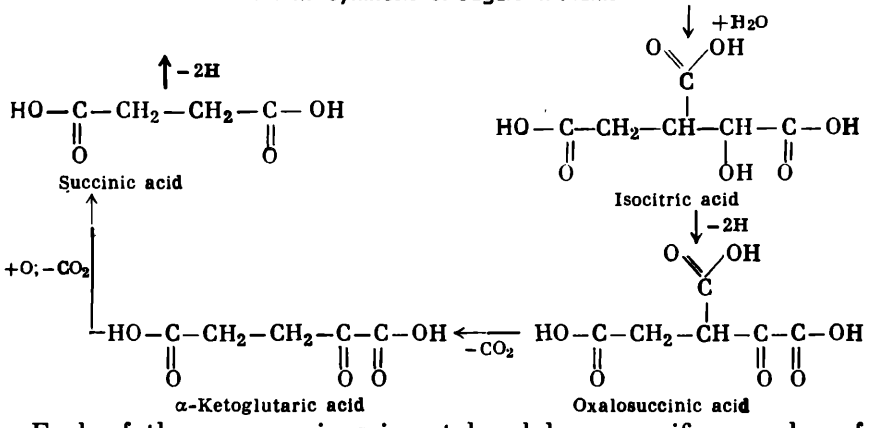
The first stage of the Krebs cycle is the above-mentioned conversion of pyruvic acid into acetyl coenzyme A having an extremely active acetyl group which is capable of acetylating, say, the alpha-carbon of oxaloacetic acid, converting the latter into citric acid.

Coenzyme A has a complicated structure which includes successively linked residues of the heterocycle adenine and the phosphoric ester of pentose (ribose), a residue of pyrophosphoric acid, which is joined to the residue of pantothenic acid, which in its turn acetylates thioethanolamine. The structure of coenzyme A will be discussed in Volume IV. When acted on by oxygen in the presence of the corresponding enzymes, pyruvic acid is decarboxylated and oxidized, and acetylates coenzyme A at sulphur:

$$CH_3-C(=O)-C(=O)-OH + {}^1/_2O_2 + CoA-SH \longrightarrow CH_3-C(=O)-S-ACo + CO_2 + H_2O$$

The entire Krebs cycle may be written as follows:



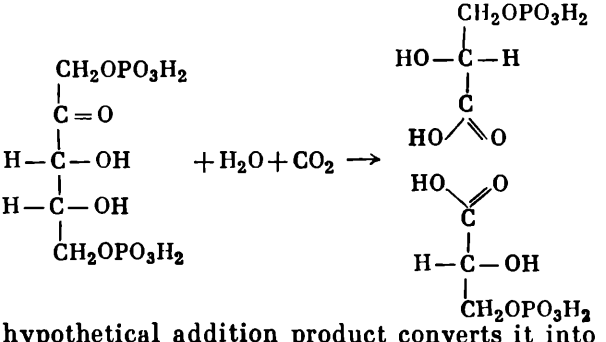


Each of these conversions is catalysed by a specific complex of enzymes. The cycle starts and ends with oxaloacetic acid, and pyruvic acid, as is easily seen, being converted at one of stages into acetyl coenzyme A, is in the long run oxidized to CO_2 and H_2O.

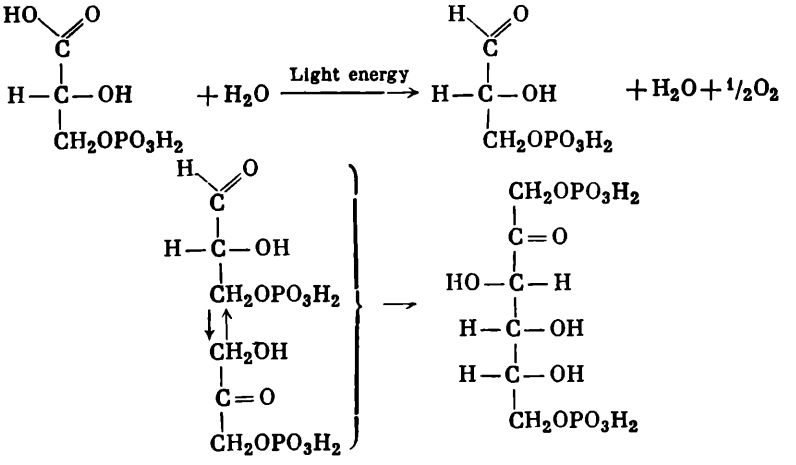
XVIII. Synthesis of Sugars in Plants

In recent years the general picture of photosynthesis in the green leaf of plants has been somewhat clarified. The **photosynthesis of carbohydrates** from carbon dioxide and water ($6CO_2 + 6H_2O \rightarrow \rightarrow C_6H_{12}O_6 + 6O_2$) is accomplished under the influence of the energy of sunlight, the utilization of which by plants is assisted by the green pigment—chlorophyll (see Volume IV).

It is interesting to note that, as shown by experiments with labelled oxygen, all the water oxygen participating in the reaction is evolved in the free state (A. P. Vinogradov). As might be expected, the process of assimilation of carbon dioxide, which has been disclosed by a number of investigators, notably by M. Kalvin, has been found to be more complicated than the reaction given above. Carbon dioxide reacts with the diphosphate ester of ketopentose—ribulose,



and via a hypothetical addition product converts it into two molecules of the phosphoric ester of D-glyceric acid. The latter is reduced by light to the **glyceraldehyde** phosphate:



The final stage of the Krebs cycle is the synthesis of the diphosphate of D-fructose by the aldol condensation of the phosphate of glyceraldehyde with the dihydroxyacetone phosphate and is completely analogous to the synthesis of a mixture of D-fructose and D-sorbose, the only difference being that it proceeds entirely stereodirectedly, like all enzymatic reactions. It is noteworthy that the reaction is the reverse of the splitting of aldol into the original reactants at the first stage of alcoholic fermentation, when the fructose diphosphate is cleaved into the phosphoric esters of glyceraldehyde and dihydroxyacetone (page 132 et seq.). This principal pathway of photosynthesis is accompanied by another process: the ribulose diphosphate required for the further assimilation of carbon dioxide is regenerated from a certain portion of the fructose phosphate.

B. Oligosaccharides. Disaccharides and Trisaccharides

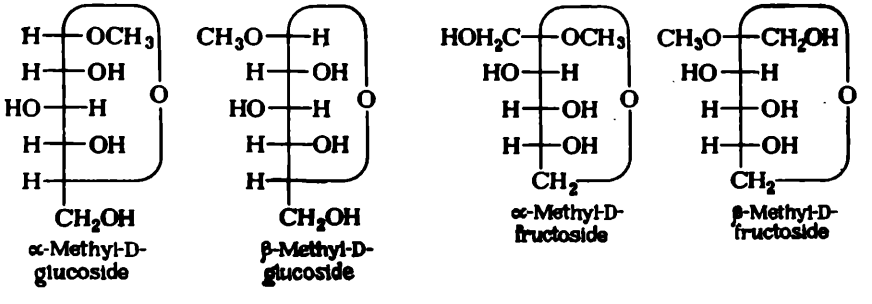
It has already been pointed out that, apart from monoses (or monosaccharides), other sugars, which are very similar in properties to monosaccharides are also found in the vegetable and animal kingdoms; on hydrolysis by weak acids or enzymes they are converted into monosaccharides. On the basis of this fact, analytical data and molecular weight determinations it has been established that such **oligosaccharides** are the anhydride forms of two or, less often, of three or four molecules of monoses. Since the hydrolysis of oligosaccharides to monoses takes place in acid but not in alkaline medium (page 142), it is clear that monoses are combined into these more complex molecules by the acetal (glycoside) linkage. Further in the text we shall be primarily concerned with **disaccharides**, i.e., the

commonest of the oligosaccharides, which, as their name implies, are formed from two monosaccharides or from two molecules of the same monosaccharide by elimination of a water molecule.

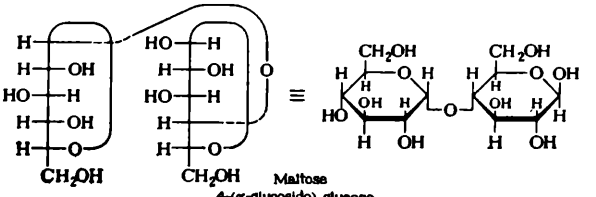
Disaccharides (like all oligosaccharides) can be divided into two groups. Those disaccharides in which both of the carbonyl groups are involved in the linkage and which therefore show no reaction for the carbonyl group (with hydroxylamine, phenylhydrazine, hydrocyanic acid, Fehling's solution, an ammoniacal solution of silver oxide, etc.) are **non-reducing disaccharides.** We shall mention only saccharose or sucrose (cane or beet sugar) and trehalose. Since glycosides show none of these reactions either, it becomes clear that the linkage between two monosaccharides in these disaccharides is glycosidic on both sides.

Disaccharides which show such reactions for the carbonyl group, but only with one half of the molecule, i.e., the reagent is used up in terms of 1 mole for 1 mole of the disaccharide, are **reducing disaccharides.** It follows from here that one molecule of the monosaccharide in them is joined through its glycoside hydroxyl and in the other molecule the glycoside hydroxyl is left intact. Therefore, the tautomerism of the cyclic form with the carbonyl form is retained and the reactions for carbonyl groups are positive.

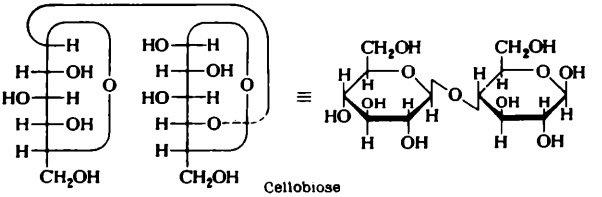
The problem of the identity of the component monosaccharides in a disaccharide is solved by the acid hydrolysis and the isolation of the individual monosaccharides or their characteristic derivatives from the hydrolytic products. Even these reactions throw light on the structure of disaccharides, though the picture has not yet been fully clarified. Let us recall that the simplest methyl glycoside has the following structure and configurations for the concrete cases of D-glucose and D-fructose:



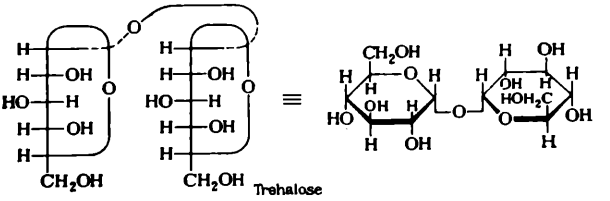
As has already been mentioned, in disaccharides formed by one molecule of glucose or fructose and one molecule of another sugar, the latter occupies the place of the methyl group in the methyl glycoside. It thus becomes apparent that two stereoisomers (α- and β-) are possible for any disaccharide. If the compound is a **non-**



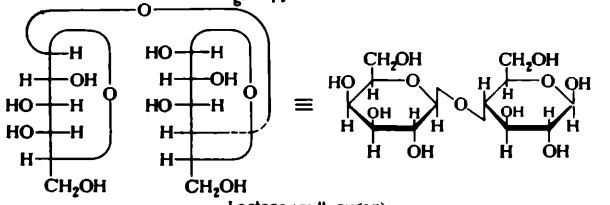
Maltose
4-(α-glucosido)-glucose
4-(α-glucopyranosyl)-D-glucose
(β-anomer of maltose)



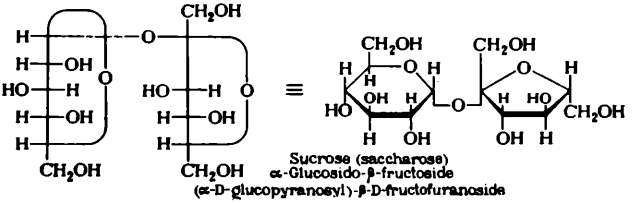
Cellobiose
4-(β-glucosido)-glucose
4-(β-D-Glucopyranosyl)-D-glucose
(β-anomer of cellobiose)



Trehalose
α,α-Glucosidoglucoside
1-(α-D-glucopyranosyl)-α-D-glucopyranoside



Lactose (milk sugar)
4-(β-galactosido)-glucose
4-(β-D-galactopyranosyl)-D-glucose
(β-anomer)



Sucrose (saccharose)
α-Glucosido-β-fructoside
(α-D-glucopyranosyl)-β-D-fructofuranoside

reducing disaccharide (i.e., contains no free aldehyde or keto group responsible for the reducing action), it means that the second monosaccharide molecule too has reacted by its glycosidic hydroxyl. Such disaccharides are known as **glycosidoglycosides**. For instance, a disaccharide of this type, made up of two molecules of glucose, is called a glucosidoglucoside; one consisting of glucose and fructose (sucrose) is termed a glucosidofructoside, etc. Depending on the configurations of the first carbon atoms of both monosaccharides, such disaccharides may have different configurations: there may exist α,α-, β,β-, and also α,β-glycosidoglycosides, and in the case of different monosaccharides, β,α-glycosidoglycosides are also possible. If the compound is a reducing disaccharide, it means that the second monosaccharide molecule has reacted by one of its alcoholic hydroxyls and its glycosidic hydroxyl is free, and therefore tautomerism with the carbonyl form is retained.

Which of the two alcoholic hydroxyl groups of the second monosaccharide molecule participates in the formation of the linkage with the first molecule? Disaccharides and other oligosaccharides with all types of linkage (through all the free hydroxyls) are well known. In oligosaccharides of animal origin the linkages are most frequently formed through the fourth and sixth hydroxyls; in oligosaccharides of vegetable origin and in those found in microorganisms the linkages are most often realized through the second and third hydroxyls. Let us write the formulas of some of the most important disaccharides and show how this and other details of their structure are established. Fischer projection formulas, Haworth perspective formulas and the names according to all the systems of nomenclature are given on p. 140.

After what has been said about the determination of the structure of disaccharides, it remains to find out the following:

1a. Which of the constituent monosaccharides (in the case of non-reducing disaccharides) plays the role of a glycoside and which, that of a glycose? In other words, which of the monosaccharides participates in the formation of the mutual linkage by its glycosidic hydroxyl, and which, by its alcoholic hydroxyl?

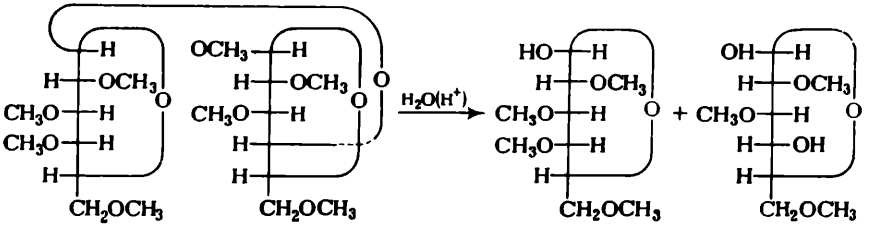
1b. Which of the alcoholic hydroxyls of the second monosaccharide is involved in the linkage?

2. Regardless of whether we deal with a reducing or a non-reducing disaccharide, it is necessary to find out how each of the monosaccharides forms a ring—in the δ-position, i.e., a six-membered ring, or in the γ-position, i.e., a five-membered ring; speaking in different terms, in those suggested by Haworth, who solved these problems by his own method, is each of the monosaccharides a pyranose or a furanose?

3. Is the disaccharide an α- or β-glycoside?

The answer to question 1a is afforded by the methylation of a disaccharide with dimethyl sulphate in alkaline solution to form an octamethyl biose (i.e., by the methylation of all the free hydroxyls) with subsequent hydrolysis which yields two methylated monosaccharides.

Lactose may be examined as an example of structure proof:



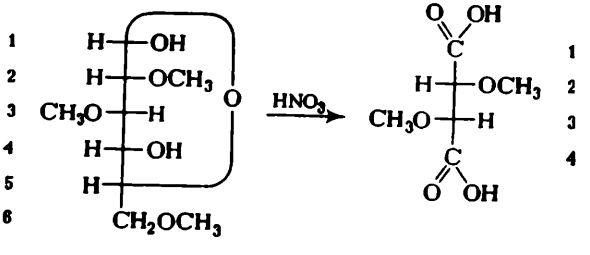
Octamethyl-lactose — Tetramethylgalactose — Trimethylglucose

In the example given, if the compound is a reducing disaccharide, and, hence, there is one free glycosidic hydroxyl, this hydroxyl is methylated.

On hydrolysis the ether bonds are not broken, whereas the glycosidic (acetal) linkages are disrupted; in particular, this glycosidic methyl group is also removed in the form of methanol. Therefore one of the methylated monosaccharides obtained as a result of hydrolysis, carries four ether groupings (four methyl groups). This is precisely a glycosidic monosaccharide. The other one, glycosic monosaccharide, bears three methyl groups.

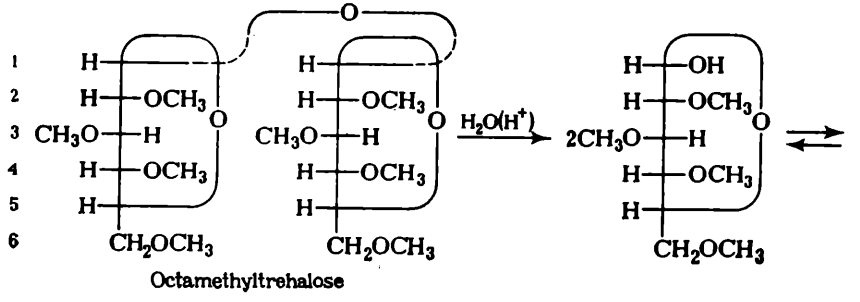
In the methylation of a disaccharide, such as trehalose or sucrose (non-reducing disaccharides), each of the two monosaccharides has four methyl groups after hydrolysis, which once again serves as an additional proof that the alcoholic hydroxyls have not taken part in the binding of the monosaccharides into a disaccharide and that this linkage is formed through both glycosidic hydroxyls.

The question 1b is answered by the oxidation of the trimethylmonose obtained (trimethyl glucose in the case of lactose given above). It has only one free alcoholic hydroxyl and one glycosidic hydroxyl, and the oxidation by nitric acid (Haworth) naturally involves these two hydroxyl groups:



The presence of the dimethyl ether of L-tartaric acid among the oxidation products of trimethylmonose is evidence that carbon-4 was sensitive to oxidation (i.e., the one carrying a hydroxyl group). This means that the glycosidic oxygen of the first (glycoside) monosaccharide was linked to this carbon atom.

In the case of trehalose, the oxidation product has been found to be trimethoxyglutaric acid (namely, the so-called *xylo*-trimethoxyglutaric acid):



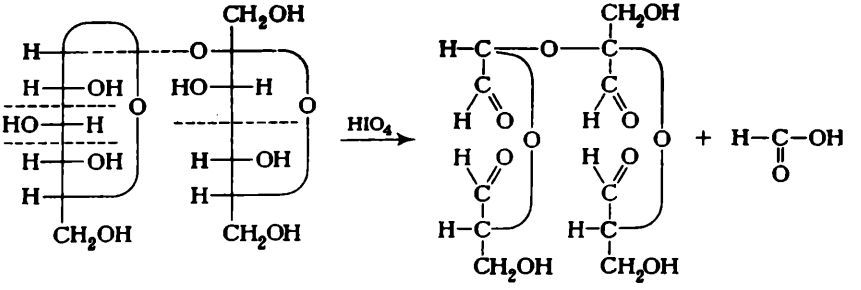
Here the oxidation at carbon-5 is due to the tautomeric opening of the pyranose ring and not to the union of two monoses, which follows from the fact that both methylated glucoses (after hydrolysis) are trimethyl glucoses.

A clue has thus been found to the solution of the second problem (the question as to whether the monosaccharides making up a disaccharide have a pyranose or a furanose ring). An answer to this question is also afforded by the oxidation of the products of hydrolysis of octamethyl bioses. But the answer will not be quite unambiguous if the hydrolysis of an octamethyl biose gives a trimethyl monose since it will have two alcoholic hydroxyls and one glycosidic hydroxyl, and it will not be clear, without indirect considerations, which of the hydroxyls becomes free as a result of the tautomeric rupture of the ring and which, as a result of the hydrolysis of the linkage between the two monosaccharides.

An additional proof can be provided by the direct oxidation of a disaccharide by periodic acid, HIO_4, a method which is also used for determination of the position of the oxygen bridge in monosaccharides.

Periodic acid quantitatively oxidizes polyhydric alcohols (with free hydroxyls), in which the hydroxyl groups are attached to contiguous carbon atoms. In this reaction, all the carbon-carbon bonds between the hydroxyl-bearing carbon.atoms are cleaved, each leaving CH_2OH group* is converted into formaldehyde, and the splitting CHOH group changes to formic acid.

For example, the periodate oxidation of sucrose proceeds as follows:



This proves the γ-closure (in other words, the presence of a five-membered furanose ring) in fructose bound into sucrose. This is a rule. Free fructose has a six-membered (pyranose) ring—the ring has been closed at position 6. In disaccharides containing fructose, and also in the corresponding polysaccharides, its ring is five-membered, being closed in position 5.

At present, all the three problems—the distinction between glycoside and glycose monosaccharides, the determination of the hydroxyl group engaged in the glycosidic linkage, and the size of the oxide ring in a monosaccharide—are very easily solved with the aid of mass-spectrometry (see page 289).

Lastly, the third question, whether the first carbon atom in disaccharides has the α- or β-configuration, is most simply answered by enzymatic hydrolysis. There are enzymes capable of hydrolysing only alpha-forms (e.g., the enzyme maltase); other enzymes (for example, emulsin) hydrolyse only beta-forms.

The properties of some monosaccharides and disaccharides are listed in Table 4.10.

The principles of building-up of trisaccharides and tetrasaccharides are the same as for disaccharides; the methods employed for their investigation are also the same. Many of these oligosaccharides occur in plants. For example, **raffinose**, *melitose* or *melitriose*, which

* The group CH_2OH adjacent to the group $\begin{array}{c}|\\ C—OH\\ |\end{array}$ is of course meant here.

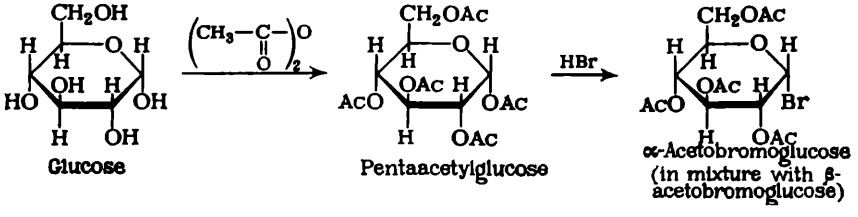
TABLE 4.10. The Properties of Monosaccharides and Disaccharides

Name	Melting point °C	Specific rotation $[\alpha]_D^{20}$ in water*, degrees	Solubility in water at 25°C, g/100 ml	Sweet taste with sucrose as reference compound (100)
Monosaccharides ($C_6H_{12}O_6$)				
α-Allose	128-128.5	−0.2 → +14.4	—	—
β-Allose				
α-Altrose	103-105	69 → +33.1	—	—
β-Altrose				
α-Mannose	133	+29.3 → +14.2	248 (at 17°C)	—
β-Mannose	132	−17.0 → +14.2		
α-Glucose	146	+112.2 → +52.7	82	74
β-Glucose	148-150	+18.7 → +52.7	154 (at 15°C)	—
α-Talose	133-134	+68 → +20.8	—	—
β-Talose	120-121	+13.2 → +20.8	—	—
α-Galactose	167	+150.7 → +80.2	68.3	32
β-Galactose		+52.8 → +80.2		
α-Gulose	Syrup	−20.4	—	—
β-Gulose				
α-Idose	Syrup	+53.0	—	—
β-Idose				
β-Fructose	102-104	−132.2 → −92.4	—	175
Disaccharides ($C_{12}H_{22}O_{11}$)				
Sucrose	186 (dec.)	66.53	—	100
α,α-Trehalose	203	197	—	—
β,β-Trehalose		−41.5	—	—
β-Maltose (hydrate)	102 (dec.)	+111.7 → +130.4	108	32
β-Cellobiose	225	+14.2 → +34.6	—	—
α-Lactose (milk sugar) (hydrate)	202	+85.0 → +52.6	17 (at 20°C)	16
β-Lactose	252	+34.9 → +55.3	—	—
β-Gentiobiose	195	+5.9 → +9.8	—	—

* The arrows connect the initial and final values of $[\alpha]_D^{20}$ for mutarotating sugars.

is found in a certain amount in sugar beet is 6-(α-D-galactopyranosyl)-α-D-glucopyranosyl-β-D-fructofuranoside; **gentianose** is 6-(β-D-glucopyranosyl)-α-D-glucopyranosido-β-D-fructofuranoside. **Cellotriose** is made up of three molecules of glucose, just as cellobiose, and is thus 4-[4-(β-D-glucopyranosyl)-β-D-glucopyranosyl]-D-glycopyranose. Another method of investigation of tri- and tetrasaccharides is based on the partial hydrolysis leading to the formation of mono- and disaccharides. Thus, raffinose subjected to partial hydrolysis forms galactose and sucrose.

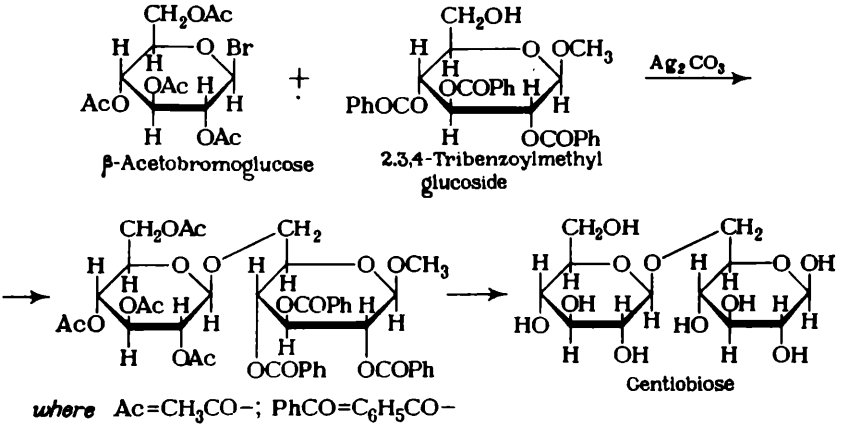
By acetylating monosaccharides with acetic anhydride, they are converted into pentaacetyl monosaccharides in which one of the acetylated hydroxyl groups is glycosidic. This acetoxyl at carbon-1 is replaced by halogen through the action of hydrogen chloride or bromide on pentaacetyl monosaccharides. The resulting compound called **acetohalogenose** or acetylhalogenomonose is widely used in the synthesis of disaccharides and other simple and complex glycosides. For instance, for glucose the reactions proceed as follows:



where Ac is the acetyl group, CH_3CO—.

The synthesis of disaccharides through the action of acetobromoglucose on monosaccharides in alkaline solution was first accomplished by A. A. Kolly (1879, Moscow) and later extended by E. Fischer. But this is not a directed synthesis since it is impossible to replace any alcoholic hydroxyl of a monosaccharide at wish, and one has to be satisfied by what is produced.

If all the hydroxyls in the molecule of the monosaccharide, except for the one that must be bound with the molecule of acetobromoglucose, are protected by some method, the desired structure will be obtained, which should then be freed from the protecting groups. The protecting groups used are the acetyl (CH_3CO) and benzoyl (C_6H_5CO) residues. The interaction of acetobromoglucose with the second molecule of the monosaccharide, which has one unprotected hydroxyl group, leads to disaccharides (the Königs-Knorr method). Helferich accomplished the synthesis of gentiobiose from β-acetobromoglucose in the following way:



The protection of the hydroxyl groups of a monosaccharide (except one) in the reaction with acetobromoglucose is also effected by way of formation of ketals with acetone, just as in the synthesis of ascorbic acid (page 127).

The action of hydrochloric acid on glucose gives rise to a host of disaccharides (gentiobiose, cellobiose, maltose, trehalose, etc.) which can be separated chromatographically in the form of acetates.

The directed syntheses of disaccharides can be accomplished by means of enzymatic catalysis, but the yields are low. As any catalyst, an enzyme speeds up a reaction in both directions (in the forward and the reverse direction). Therefore, enzymes that catalyse the hydrolysis of disaccharides to monosaccharides also catalyse the synthesis of the same disaccharides from the monosaccharides. Indeed, maltose was obtained as far back as 1902 by the action of yeast enzymes on a concentrated solution of glucose (such concentrated solutions are not subject to fermentation). Gentiobiose was prepared by the action of the enzyme emulsin (from bitter almonds) on a concentrated solution of glucose. The action of the enzyme phosphatase on the phosphate ester of glucose (1-phosphate) and fructose gives sucrose.

C. Polysaccharides

Polysaccharides are high-molecular-weight compounds (the molecular weight ranges from 20,000 to 1,000,000 and upwards), built up in the same manner as oligosaccharides. On complete hydrolysis in acid solution they form a large number of monosaccharide molecules. Those polysaccharides which contain only a single type of carbohydrate residue (and these are the most important ones) are called **homopolysaccharides**. The second major group of polysaccharides

is termed the **heteropolysaccharides**. These are defined as containing two or more different carbohydrate units. Homopolysaccharides include starch and its varieties—amylose and amylopectin, glycogen, cellulose, inulin; examples of heteropolysaccharides are so-called hemicelluloses, plant gums, numerous polysaccharides contained in microorganisms. Polysaccharides may be subdivided, in each of the two main headings, into two categories: straight-chain polysaccharides (e.g. cellulose) and branched-chain polysaccharides (e.g. starch).

Starch (*Amylum*). Starch and glycogen play an especially important role in biological processes. Starch is the principal food reserve carbohydrate of plants. It is stored as granules in the grains of cereals and other seeds and roots of plants, in the tubers of potatoes, and when the grains are sprouting it is hydrolysed enzymatically to soluble oligo- and monosaccharides (maltose or glucose) and is utilized in this form by plants for growth and energy purposes. The sprouting grains of cereals contain such a large amount of the starch hydrolysis enzyme (diastase) that dried and ground barley sprouts (malt) are used for saccharifying the "foreign" starch of potatoes or corn (maize) (conversion into maltose) in the production of alcohol or beer (the maltose is then fermented). Under the microscope the starch grains may be seen to consist of an inner nucleus (hilum), around which are deposited concentric layers. Starch is not an individual substance. It consists of the water-soluble fraction, called **amylose**, which forms moderately viscous solutions and gives a pure blue colour with iodine, and the fraction, called **amylopectin**, which is insoluble in cold water but forms a very viscous paste ("starch paste") with hot water and gives a red-violet colour with iodine. Like any high-molecular-weight compound, both amylopectin and amylose are not, strictly speaking, individual entities. They are mixtures of polymer-homologues (see Volume I, page 192). The most usual forms of starch are potato flour and rice starch. Potato flour is produced by mechanical destruction of the tuber cells of potatoes and by swelling the starch granules in water, the grains being settled to the bottom.

The partial hydrolysis of starch, which is achieved by heating with the water adsorbed by it, yields a mixture of products known as **dextrins** which are of various molecular weight. But their molecular weights are invariably much lower than the molecular weights of amylopectin and amylose. Dextrins are soluble in water and, depending on molecular weight, give blue, violet, red, orange-red and yellow colours with iodine. The dextrin solution known as mucilage is used as an adhesive for paper and as a sizing material for textiles.

Starch is the principal constituent (by weight) of food for man (bread, potatoes, groats, vegetables) and is the main energy resource of the human organism. The percentage content of starch in some

foods rich in starch is as follows: 74 in flour; 78 in rice; 51 in white bread; 16 in potatoes. Even when in the mouth, starch undergoes hydrolysis under the action of saliva containing the hydrolytic enzyme amylase. The hydrolysis ends in the stomach with the breakdown of starch to glucose which is brought from the intestine into the blood and is carried by the blood stream to the cells of the body where it undergoes a number of transformations (page 132) responsible for the heat of the body, the energy of the muscular and brain functioning in human beings and animals. A strictly definite concentration of glucose is to be maintained in the blood: both a considerable excess and, especially, a deficiency of glucose is fatal to the organism. The concentration of glucose is controlled by the action of hormones. With an increased content of glucose in the blood, an excess of glucose is accumulated, due to the specific action of insulin (a protein, see Volume IV) excreted by the pancreas, in the liver and partly in the muscle tissue in the form of **glycogen** (*animal starch* or *liver starch*). The liver tissue may contain up to 20 per cent by weight of glycogen. If the blood is glucose-deficient, part of the liver glycogen is hydrolysed to glucose and enters the blood stream (the hormone glucagon). If the functioning of pancreas is disturbed and it does not produce insulin, a sugar disease or diabetes begins, which is characterized by the increased content of glucose in the blood. The organism has to get rid of excess glucose with urine. The regular injection into the blood of the insulin isolated from the pancreas of animals restores the regular functioning of glucose in the blood.

Inulin. A fructose polysaccharide found in dahlia and Jerusalem artichoke tubers. It is an analogue of starch and is built from D-fructose units. Inulin is hydrolysed in the stomach to fructose and is thus as nutritious as starch.

Cellulose. Cellulose forms the chief constituent of the cell walls of all plants. Cotton wool and filter paper consist almost entirely of cellulose (the finest Swedish filter paper is an almost chemically pure form). Wood contains approximately 50 per cent of cellulose which is combined with lignin, a high-molecular-weight aromatic compound of phenolic character (see Volume IV).

Native cellulose has a molecular weight of at least 2,000,000; the number of glucose residues exceeds 10,000 (O. P. Golova).

The production of cellulose from wood on a large industrial scale is accomplished by two principal methods.

1. *The sulphite process.* The major proportion of writing paper (stationery) and print paper is made from sulphite cellulose. Spruce wood is treated on heating and under pressure with calcium disulphite. In this process, the aromatic phenol rings of lignin add on sulpho groups; the resulting ligninsulphonic acids dissolve in water ("sulphite liquor"), leaving lignin-free cellulose in the form of fibres which is used for the production of various kinds of paper, synthetic

fibre and for the manufacture of plastics and gun powders. Because of the weak acidity of the medium there takes place a partial hydrolysis of the cellulose chains and a cellulose with a lower molecular weight is formed (the number of glucose residues in the macromolecule being a few hundreds).

2. *The sulphate process.* In this process (also known as the *kraft process*), use is made of any woody plant—coniferous, foliate and mixed woods. The wood is treated with a mixture of alkali and sodium sulphate resulting from the reduction (calcination) of natural sodium sulphate with organic residues (lignin) left from the previous portion of sulphate cellulose. Lignin dissolves in this alkaline solution and cellulose is left, which is destroyed to a lesser degree than in the sulphite method, since it is not hydrolysed in alkaline medium. The resulting pulp (kraft pulp) is stronger than the sulphite process pulp and is utilized for producing the strong brown paper (kraft paper) used for boxes, bags, wrapping paper, and other containers.

(a) *Structure of Polysaccharides*

An investigation into the structure of homopolysaccharides consists of the following steps.

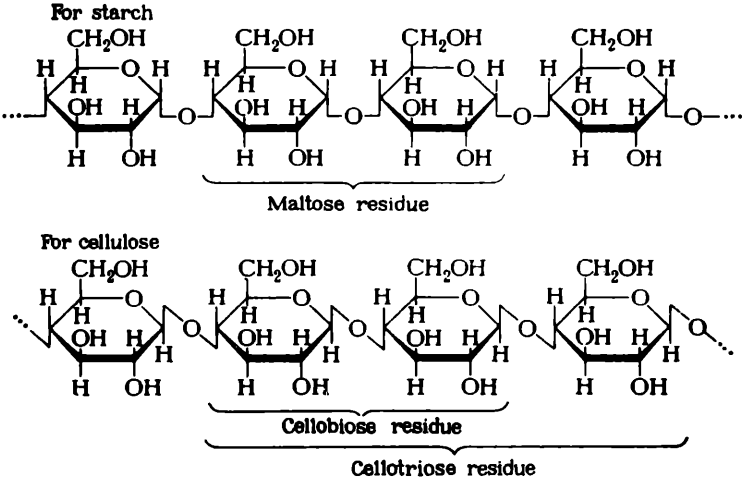
1. Complete hydrolysis of a polysaccharide and identification of the monosaccharides which are the structural units of the macromolecule.

2. Establishment of the presence of branches in the main chain of the polysaccharide, of the types of bond between the monosaccharide units and of the size of the oxide rings of each of the sugars involved. This is usually achieved by using the methylation method, the periodic acid oxidation of the polysaccharide and partial hydrolysis by dilute acids, which enables the isolation of small fragments of the polysaccharide chain.

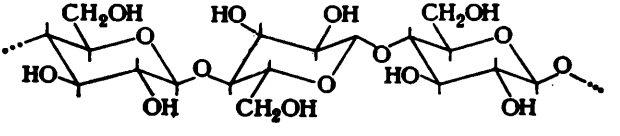
3. Enzymatic hydrolysis (complete or partial) with the purpose of elucidating the configuration (α - or β-) of carbon-1 (or carbon-2 in ketoses).

Incomplete hydrolysis of a polysaccharide yields a mixture of oligosaccharides, which are examined in the same way as described for disaccharides (methylation, hydrolysis, oxidation of the resulting trimethyl and tetramethyl monoses). The investigation of starch and its constituents (amylose and amylopectin) has shown that their structure is similar to that of maltose, i.e., that they have the α-glucosido-(glucosido)$_n$-α-glucose constitution. Cellulose which, like starch, forms only glucose on hydrolysis, has been found by this method to have the β-glucosido-(glucosido)$_n$-β-glucose structure. The linkage between the glucose units in cellulose is consequently the same as in the products of its partial hydrolysis (cellobiose and cellotriose).

The portions of the macromolecules of starch and cellulose may be represented by the following schemes:

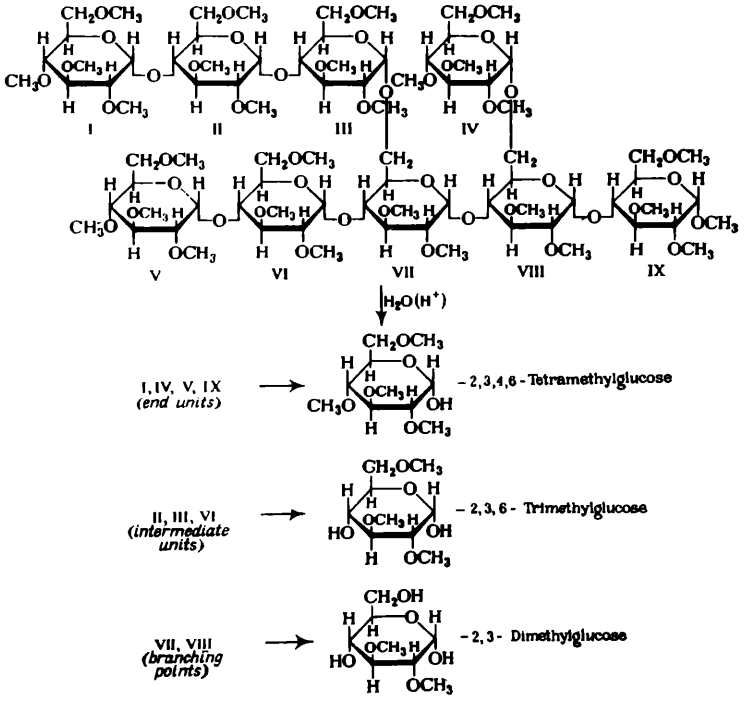


The perspective representation of a section of the cellulose macromolecule, in which the rings are drawn in such a way as to show the conformations of the rings in the chair form, is as follows:



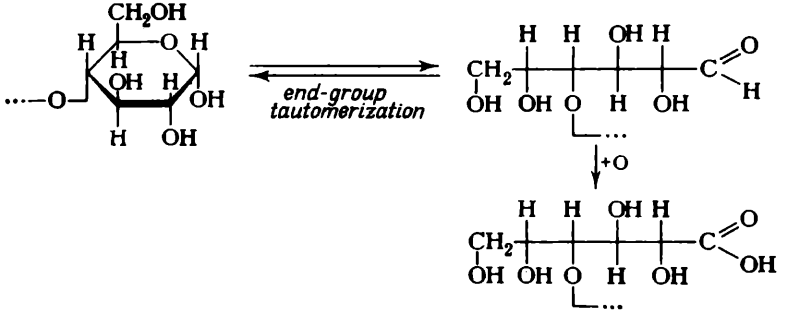
A more detailed study of the various fractions of starch (amylose and amylopectin) and glycogen shows that the hydrolysis, say, of the completely methylated starch (trimethyl starch) gives not only 2,3,6-trimethylglucose (the hydrolysis of the medium units of the macromolecule) but also 2,3,4,6-tetramethylglucose (evidently, due to the hydrolysis of the terminal glucose units). Besides, 2,3-dimethylglucose is also obtained, the presence of which indicates that the primary alcoholic group (carbon-6) of some glucose units is not free (and cannot therefore be methylated), which serves as an evidence

for the presence of branches in the macromolecules of starches:



The degree of branching of starch can be deduced from the relative amount of 2,3-dimethylglucose, and the number of terminal groups and, hence, the average chain length, can be determined from the amount of 2,3,4,6-tetramethylglucose.

Another method used to determine the number of terminal groups is based on the determination of the reducing properties of unmethylated starches, these properties being due to the presence of terminal groups with a free glycosidic hydroxyl:



It is easy to see that the determination of the quantity of 2,3,4,6-tetramethylglucose in the methylation products of starch gives the content of terminal glucoside and glucose groups, while the reduction method provides information on the number of glucose groups only.

From the data obtained by all these methods and by molecular-weight determinations it is possible to arrive at the conclusion that the water-soluble fraction of starch (amylose) has unbranched chains of about 1000 glucose residues united together by the same type of linkage as found in maltose. The insoluble part of starch (amylopectin) is a highly branched polysaccharide having a much higher molecular weight (1,000,000-10,000,000) and consisting of 5000-50,000 glucose units. Animal starch, or glycogen, is the most highly branched compound among the starches, and is largely built in the same manner as amylopectin. Its molecular weight is 1,000,000-10,000,000 (5000-50,000 glucose units); its chain has branches every other three or four glucose units.

The molecules of glycogen and amylopectin have an almost spherical shape due to branching. Amylose molecules have a linear form but it should be understood in the sense that the glucose residues are linked together successively, without branching. X-ray analysis shows the helical coiling of the successively joined hexahedrons of amylose molecules. The well-known deep blue colour starch gives with iodine is due to the presence of amylose. It forms with iodine a typical "clathrate" compound since the iodine molecules are able to fit inside the coil and are "imprisoned" in it, forming a molecular inclusion compound of the composition $C_6H_{10}O_5I_2$.

As to cellulose, its partial hydrolysis leads, as has been mentioned above, to cellotetraose, cellotriose, cellobiose, while its complete hydrolysis gives glucose. The first three oligosaccharides are structurally similar and, unlike starch, are β-glucosido-(β-glucosido)$_n$-glucoses. The method of hydrolysis of methylated celluloses has enabled the chemists to establish the practically complete absence of 2,3-dimethylglucose, i.e., the absence of branches. The weak reducing power of cellulose itself and the small amount of 2,3,4,6-tetramethylglucose in the products of hydrolysis of the completely methylated cellulose are evidence for the large length of its chains. Cellulose is insoluble in water and organic solvents but dissolves in Schweitzer's reagent, an ammoniacal solution of copper hydroxide, $[Cu(NH_3)_4](OH)_2$. By using Staudinger's method, in which the viscosity of such solutions is determined (avoiding any contact with air which can oxidize and hence disrupt the cellulose chains), it is possible to establish the molecular weights of various cellulose preparations.

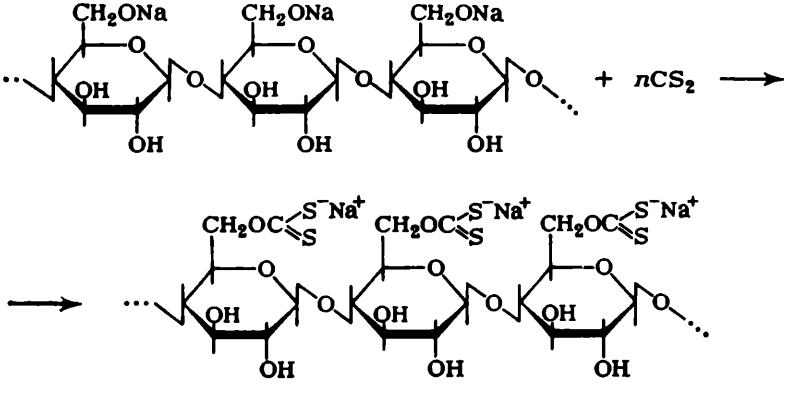
Of no less practical importance than the chemical constitution of cellulose is the so-called "secondary structure", i.e., the rigid confor-

mation of individual macromolecular chains and their packing into bundles, which provide a picture of crystallinity according to X-ray analysis data.

(b) *Derivatives of Cellulose*

When cellulose is treated with concentrated alkali, the hydrogen of the primary hydroxyl group is replaced in each glucose residue by sodium and **alkali cellulose** is produced; and treatment with water regenerates cellulose with its secondary structure changed, the cellulose being called **hydrocellulose**. The process is known as **mercerization*** and is widely employed in the textile industry for imparting a silky lustre and better dye affinity to fabrics.

The action of carbon disulphide on alkali cellulose, produced directly from wood, gives a cellulose xanthate:



The xanthate is soluble in water, and the resulting solutions of the high-molecular-weight compound are highly viscous (hence the name of **viscose**). When the viscose solution is forced through fine spinneret holes into a bath of sulphuric acid, carbon disulphide is eliminated and cellulose is regenerated in the form of very fine filaments which are stretched by winding them up on bobbins. In this way **viscose rayon**** is produced. This is the main process (known as the viscose or xanthate process) in the production of synthetic fibre for textile fabrics and for technical purposes (tyre cord).

Another, older method of production of synthetic fibre, called the cuprammonium process, which is no longer of any great com-

* After its discoverer, John Mercer.—*Tr.*

** Viscose rayon was discovered by the English chemists Cross and Bevan in 1892.—*Tr.*

mercial importance, consists in forcing a solution of cellulose in Schweitzer's reagent through holes into a bath containing sulphuric acid. As the copper-ammonia-cellulose complex is destroyed, filaments of regenerated cellulose are precipitated.

When cellulose is submitted to alkylation, a trialkylcellulose is formed on maximum substitution (three alkyl groups per glucose unit). The alkylation of cellulose is employed for the manufacture of polymeric materials.

The treatment of cellulose with acetic anhydride results in the formation of cellulose triacetate. Unlike cellulose itself, this compound is soluble in acetone and esters. Cellulose acetates are used for production of motion picture film, plastics and acetate silk.

When cellulose is treated with a mixture of nitric and sulphuric acids, cellulose dinitrate (**collodion** or **colloxylin**) is obtained, which is soluble in an alcohol-ether mixture. The use of concentrated nitric acid and 95-percent sulphuric acid gives cellulose trinitrate known as **pyroxylin** or **gun-cotton** which is utilized in the preparation of **smokeless powder.** Smokeless powders are obtained by gelatinization of pyroxylin through the addition of up to 30 per cent of glycerol nitrate (nitroglycerine) in the presence of a stabilizing agent, say, diphenylamine, the resulting mass being moulded into grains, lumps, or cylinders of the various shapes and sizes, depending on the type of application.

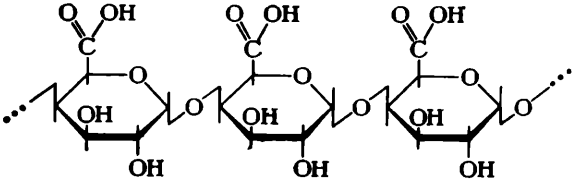
One of the ever expanding applications of wood cellulose is the acid hydrolysis to glucose which is subjected to fermentation to prepare alcohol (the hydrolysis industry). Lignin is left in the solution (hydrolysis lignin).

Dextrans. These compounds are 6-(α-D-glucopyranosyl)-(6-α-D-glucopyranosyl)$_n$-D-glucoses in which the number of repeating units ranges from several tens to several hundreds. They are produced by certain bacteria growing upon sucrose. Aqueous solutions of dextrans find application in medicine as a plasma substitute in blood transfusions; they are also utilized for producing a molecular sieve (Sephadex) made by cross-linking dextran molecules.

Pentosans. Pentoses, such as xylose, arabinose, also form cellulose-like polysaccharides called **pentosans.** The shells of peanuts, sunflower seeds, maize cobs, and cereal straws are abundant sources of pentosans. The hydrolysis of such agricultural residues gives xylose.

Pectins. When galactose is oxidized at the primary alcoholic group (carbon-6) with the aldehyde group left intact, galacturonic acid is obtained, which retains a tendency towards ring-chain tautomerism characteristic of all monosaccharides. Chains having a structure like that of cellulose but built up of galacturonic acid residues (instead of glucose units as in cellulose) and having a relatively low molecular weight (20,000-200,000) are called **pectic acids** which

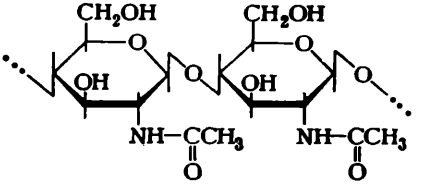
are widely distributed in plants:



Their neutral esters—**pectinic acids**—are partly responsible for the consistency of jams.

On decarboxylation pectic acid is converted into a pentosan—**araban**, a polysaccharide of arabinose (it is found associated with pectic materials). The polysaccharides of galactose known as **galactans** are also contained in pectic materials. Galactans have the structure of pectic acid, but with the CH_2OH group instead of the carboxyl group.

The exoskeletons (shells) of insects and crustaceans contain **chitin**, a polysaccharide of the cellulose type, built up of N-acetylglucosamine units:



Hemicelluloses. Wood contains alkali-soluble materials which partly pass into sulphite cellulose. These substances are so-called **hemicelluloses**, which are heteropolysaccharides of relatively low molecular weight (about 30,000). They are built like cellulose but of different monosaccharides, largely of pentoses—D-xylose, D-arabinose, but also of D-galactose, sometimes of D-mannose and D-glucose, into which they decompose on hydrolysis.

Plant Gums. Cherry gum, gum arabic, tragacanth are all plant gums. They are all heteropolysaccharides, which on hydrolysis give D-galactose, D-arabinose, less often D-xylose, and uronic acids—D-glucuronic and D-galacturonic acids.

Seaweed (Algal) Polysaccharides (Seaweed Mucilages). Seaweeds contain a very large number of heteropolysaccharides, many of which are of nutritious or commercial importance. These polysaccharides consist of the residues of galactose, mannose and other monosaccharides and also of deoxy sugars and uronic acids. Many of them are sulphuric acid esters, which contain one and, sometimes, two sulphuric acid residues per monosaccharide unit. Brown seaweeds contain

alginic acids, the structural unit of which is mannuronic acid. Galacturonic acid is the basic structural unit of the pectic materials of fruits and vegetables. Alginic acids find use as thickening agents for food. The pectic materials extracted from apples or beet are utilized for the purpose.

Polysaccharides of Animal Tissues. Widely distributed in the animal and human organism are the heteropolysaccharides which enter into the composition of connective tissues, blood, and nervous tissue. These polysaccharides contain amino sugars, mannose, galactose, uronic acids, and less often glucose. Part of the hydroxyl groups in them are also esterified by the sulphuric acid residues.

Polysaccharides of Microorganisms. The world of microorganisms is especially rich in the various heteropolysaccharides which are found to contain a wide range of monosaccharides, including amino- and deoxy sugars and other structurally more complex monosaccharides. These polysaccharides occur in the outer layers of the bacteria and control their biological specificity. It is known, for example, that each type of pneumococcuses—stimulants of pneumonia—contains a specific polysaccharide. For example, one of these polysaccharides consists of glucose and glucuronic-acid residues, and another one is built of galactose and glucosamine units.

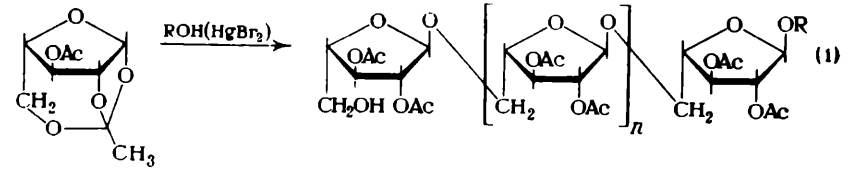
The most extensively studied are the polysaccharides of Gram-negative bacteria species which play the role of antigens inducing the production of the appropriate antibody in the animal, the antibodies then conferring immunity against the particular bacterial infection. These polysaccharides are heteropolysaccharides containing the repeating units of a tri- or tetrasaccharide; the structure of this repeating unit strictly and unambiguously specifies the microbe chemically. Polysaccharide chains are attached, through structurally complex lipids, to the outer capsule of the bacterial cell.

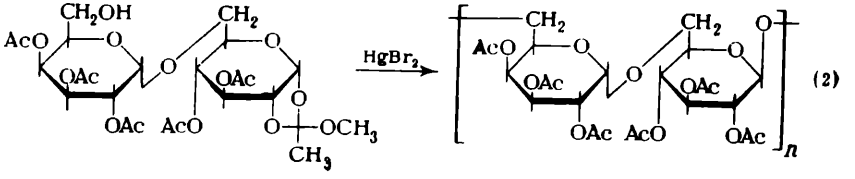
(*c*) *Synthesis of Polysaccharides*

When monosaccharides are treated with acid in aqueous solution, there is obtained a mixture of oligosaccharides and relatively low-molecular-weight polysaccharides with branched chains and a random distribution of α- and β-linkages. Higher-molecular weight polysaccharides, which are also branched-chain compounds and have the mixed α- and β-configuration, are formed by the action of gaseous HCl or phosphoric acid on monosaccharides (Fram, Yu. L. Pogosov, Z. A. Rogovin).

N. K. Kochetkov and A. F. Bochkov have synthesized polysaccharides with a definite permanent type of linkage in the chain of monosaccharide units by means of the polycondensation of orthoesters of sugars under the action of mercuric bromide in alcoholic solution (alcohol initiates the reaction).

The starting materials used are internal orthoesters (for example, the orthoester of arabinofuranose, reaction 1) or orthoesters having a free hydroxyl group in the molecule (e.g., the orthoester of galactosylglucose, reaction 2):





In this way polysaccharides with the same type of intermonomeric linkage have been prepared.

4.6. Amino Acids

Amino acids are acids in which the hydrogen of the hydrocarbon radical is replaced by the monovalent amino group $-NH_2$. A distinction is made between α-, β-, and γ-substituted acids, etc., according to the position of the substituent in the carbon chain. There are some specific methods of synthesis for each of these classes of amino acids and there are some differences in their properties. From the biological point of view, α-amino acids are of great biological importance. A number of these acids (see Table 4.11) can be derived from natural materials by the hydrolysis of proteins present in meat, skin, gelatine, wool, hair, feather, and also the proteins of protoplasm and nuclei of plant and animal cells, casein from curds, a number of hormones such as insulin, enzymes (e.g., pepsin), etc. α-Amino acids are the simplest building blocks from which the high-molecular-weight proteins, without which no life is possible, are constructed. Since proteins contain aromatic and heterocyclic α-amino acids as well as aliphatic α-amino acids, it is more convenient to consider them at the end of the course (see Volume IV).

All natural amino acids, except aminoacetic acid, contain an asymmetric carbon atom. They all belong to the L-series. The simplest β-amino acid, aminopropionic acid, enters into the composition of an important and universal vitamin—pantothenic acid (Greek: from everywhere), but in general the role of β-amino acids is incom-

TABLE 4.11. The Most Important Amino Acids of the Protein

Trivial name	Abbreviation	Formula	m. p., °C	$[\alpha]_D$ in glacial acetic acid, degrees	Isoelectric point, pH	Solubility in water at 25°C, g/100 g
Glycine	Gly	NH_2CH_2COOH	262	—	5.97	25
Alanine	Ala	$NH_2CH(CH_3)COOH$	297	+33	6.00	16.6
Valine	Val	$NH_2CHCOOH$ $\vert$ $CH(CH_3)_2$	315	+62	5.96	8.85
Leucine	Leu	$NH_2CHCOOH$ $\vert$ $CH_2CH(CH_3)_2$	337	+22.5	5.98	2.2
Isoleucine	Ileu	$NH_2CHCOOH$ $\vert$ $CH_3-CH-C_2H_5$	284	+49	6.02	4.12
Aspartic acid	Asp	$NH_2CHCOOH$ $\vert$ CH_2COOH	270	+25.4	2.77	0.5
Asparagine	Asn	$NH_2CHCOOH$ $\vert$ CH_2CONH_2	236	+34.3	5.41	2.5
Glutamic acid	Glu	$NH_2CHCOOH$ $\vert$ CH_2CH_2COOH	249	+31.8	3.22	0.84
Glutamine	Gln	$NH_2CHCOOH$ $\vert$ $CH_2CH_2CONH_2$	185	6.1 (in water)	5.65	4.2
Ornithine (+)	Orn	$NH_2CHCOOH$ $\vert$ $CH_2CH_2CH_2NH_2$	140	+11.5	—	—
Lysine	Lys	$NH_2CHCOOH$ $\vert$ $CH_2CH_2CH_2CH_2NH_2$	224 (dec.)	+25.9	9.74	Dissolves well

Table 4.11 (continued)

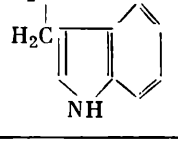
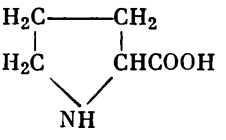
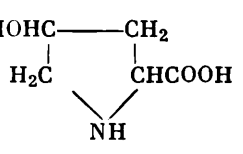
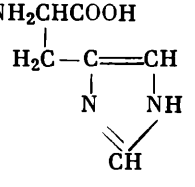
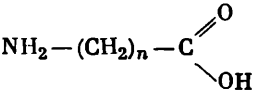
Trivial name	Abbreviation	Formula	m. p., °C	$[\alpha]_D$ in glacial acetic acid, degrees	Isoelectric point, pH	Solubility in water at 25°C, g/100 g
Arginine	Arg	$NH_2CHCOOH$ $\vert$ CH_2 $\vert$ $CH_2CH_2NH-C(=NH)-NH_2$	238	+29.4	10.76	15
Serine	Ser	$NH_2CHCOOH$ $\vert$ CH_2OH	228	+15	5.68	5
Threonine	Thr	$NH_2CHCOOH$ $\vert$ $CH(OH)CH_3$	253	−30	6.16	20.5
Cysteine	CySH	$NH_2CHCOOH$ $\vert$ CH_2SH	178	+13	5.02	Dissolves well
Cystine	CySSCy	$(NH_2CHCOOH$ $\vert$ $CH_2S-)_2$	260	−232	5.03	0.011
Methionine	Met	$NH_2CHCOOH$ $\vert$ $CH_2CH_2SCH_3$	283	+20	5.74	3.5
Phenylalanine	Phe	$NH_2CHCOOH$ $\vert$ $CH_2C_6H_5$	283 (dec.)	−7.5	3.0	—
Tyrosine	Tyr	$NH_2CHCOOH$ $\vert$ $CH_2C_6H_4OH$-*n*	344	−10	5.66	—
Tryptophan	Try		382	−34	5.89	1.14

Table 4.11 (continued)

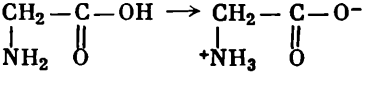
Trivial name	Abbreviation	Formula	m. p., °C	$[\alpha]_D$ in glacial acetic acid, degrees	Isoelectric point, pH	Solubility in water at 25°C, g/100 g
Proline	Pro		299	−80	6.30	16.2
Hydroxyproline	Hypro		270	−77	5.83	36.1
Histidine	His		277	+7.5	7.6	4.3

parably less important than that of α-amino acids. Of other amino acids, commercial importance has lately been attached to ω-amino acids of the general formula



where $n = 5, 6, 8, 10$. These amino acids (more exactly, their lactams) are used to produce synthetic fibres such as capron ($n = 5$). They do not occur in nature.

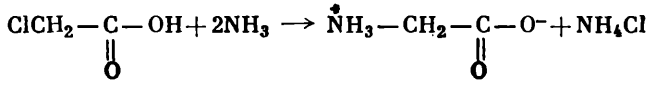
All amino acids, having an acid carboxyl group and a basic amino group in the molecule, should have been unstable, but in fact they are built as inner salts:



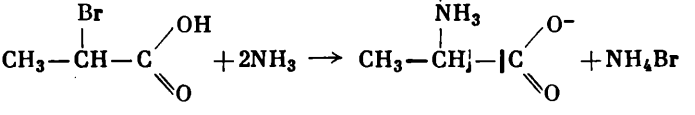
Such a structure* does not render them incapable of reacting as an acid due to the expulsion of a proton from the ammonium group, $-N^+H_3$. The ammonium ion, N^+H_4, also reacts as an acid.

A. Synthesis of Amino Acids

Synthesis of α-Amino Acids. 1. The action of excess ammonia (in aqueous solution or liquid ammonia) on α-halosubstituted carboxylic acids. For example,



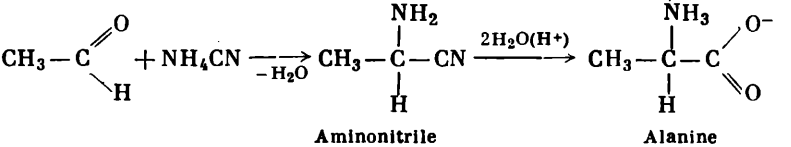
α-Aminoacetic acid (glycine, glycocoll)



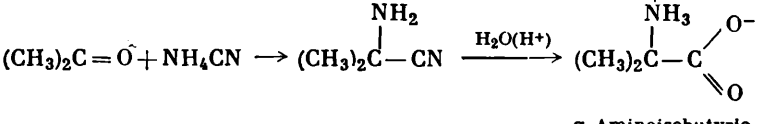
α-Aminopropionic acid (alanine)

An analogous method is in principle also applicable to the synthesis of amino acids with any distance between the amino group and the carboxyl group, but the corresponding halogen-substituted acids are generally less available than α-halosubstituted acids.

2. The hydrolysis of α-aminonitriles obtained by the action of ammonium cyanide (or of a mixture of ammonium chloride and potassium cyanide) on carbonyl compounds (Strecker, N. D. Zelinsky):



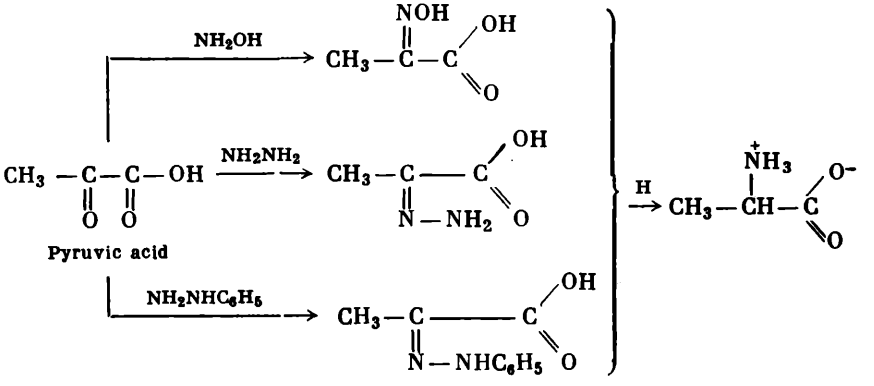
Aminonitrile — Alanine



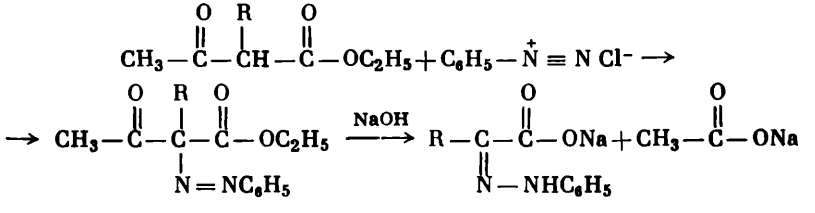
α-Aminoisobutyric acid

*Molecules which can form dipolar ions of this kind are called **zwitterions** (the German word for two ions).—*Tr.*

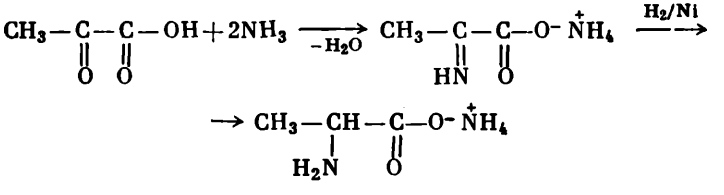
3. Reduction of oximes, hydrazones and phenylhydrazones of α-keto acids:



The phenylhydrazones of α-keto acids can also be obtained by the Feofilaktov method by the action of aromatic diazo compounds (see Volume III) on acetoacetic ester with subsequent acid cleavage (page 78):



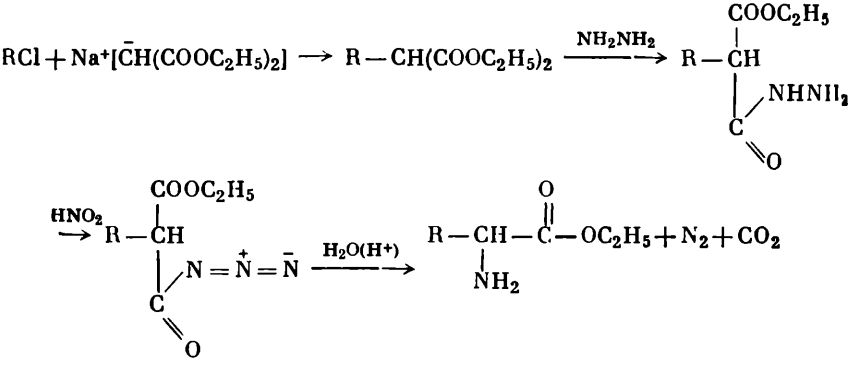
α-Amino acids can also be prepared directly from α-keto acids by the action of ammonia and hydrogen on the keto acids over a nickel catalyst:



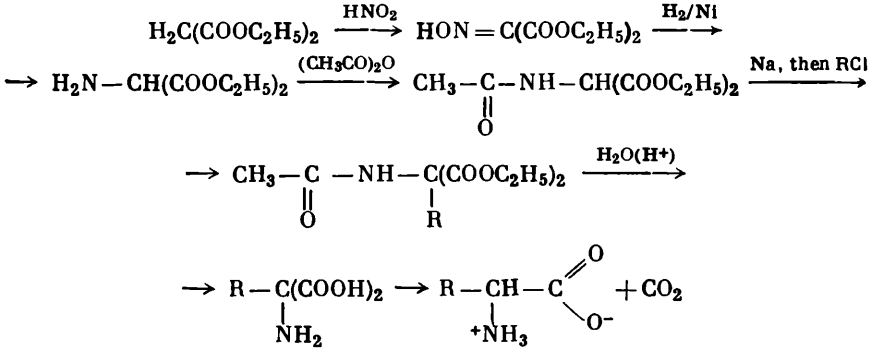
4. A number of syntheses of α-amino acids have been accomplished via malonic ester by the following routes.

(a) First, the alkylmalonic ester required for the purpose is prepared via sodiomalonic ester (see Volume I). The ester obtained is reacted with hydrazine to convert it into semihydrazide, a half-ester, which is then transformed by the action of nitrous acid into an azide, following which the azide is subjected to the Curtius rear-

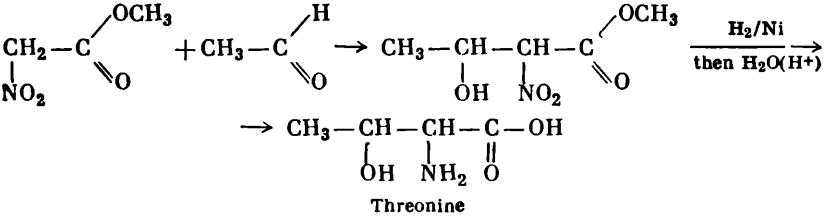
rangement (see Volume I) to give an α-amino acid:



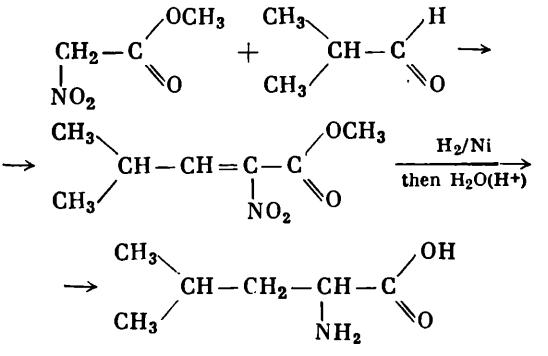
(b) Another route for synthesis via malonic ester consists of its nitrosation and subsequent reduction of the nitrosomalonic ester to aminomalonic ester. The latter is acetylated and the resulting sodium derivative is subjected to alkylation:



There are many other routes for synthesis of α-amino acids. According to the data obtained by V. M. Belikov and K. K. Babievsky, an exceedingly convenient starting material for the synthesis of α-amino acids of various structure is an ester of α-nitroacetic acid, which is converted by the condensation with aldehydes (a croton- or aldol-type condensation) and subsequent reduction into α-amino acids. For example,



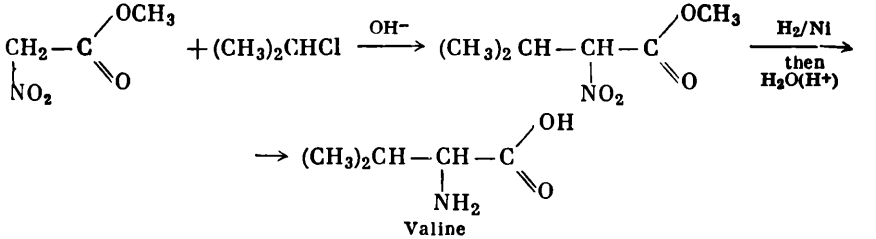
Threonine



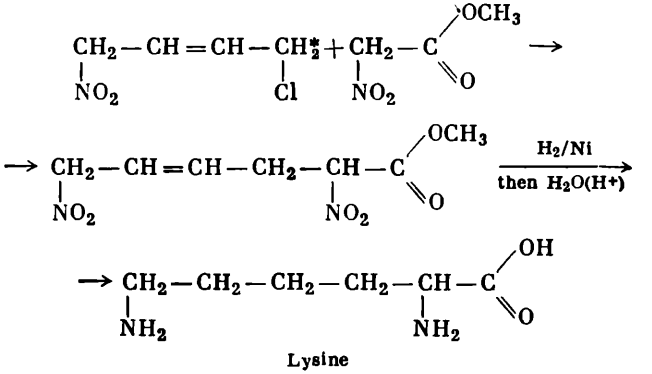
Leucine

In a similar way, by condensing the various aliphatic, aromatic or heterocyclic aldehydes, it is possible to obtain all amino acids that are the derivatives of alanine with a substituent R in the methyl group.

Conversions of nitroacetic ester can be varied by alkylating it in alkaline medium by means of an alkyl halide or, in general, by a halogen derivative (V. V. Perekalin):



Valine



Lysine

* This is the product of the 1,4-addition:

Synthesis of β-Amino Acids. 1. The most important method is the addition of ammonia to α,β-unsaturated acids:

$$CH_2=CH-\underset{\underset{O}{\|}}{C}-OH+NH_3 \longrightarrow H_2N-CH_2-CH_2-\underset{\underset{O}{\|}}{C}-O^-$$

2. V. M. Rodionov suggested a method in which the preparation of an α,β-unsaturated acid by the condensation of an aldehyde with malonic acid and the addition of ammonia are combined in a single procedure:

$$R-\underset{\underset{H}{|}}{\overset{\overset{O}{\|}}{C}} + \underset{\underset{COO^-}{|}}{\overset{COO^-}{\underset{|}{H_2C}}} + 2NH_3 \xrightarrow[-CO_2]{} R-\underset{\underset{NH_2}{|}}{CH}-CH_2-\underset{\underset{O}{\|}}{C}-O^-\overset{+}{N}H_4$$

Synthesis of γ-Amino Acids and Acids with a More Remote Position of the Amino Group. 1. The synthesis of such amino acids may be accomplished by means of Procedure 3 described above for α-amino acids.

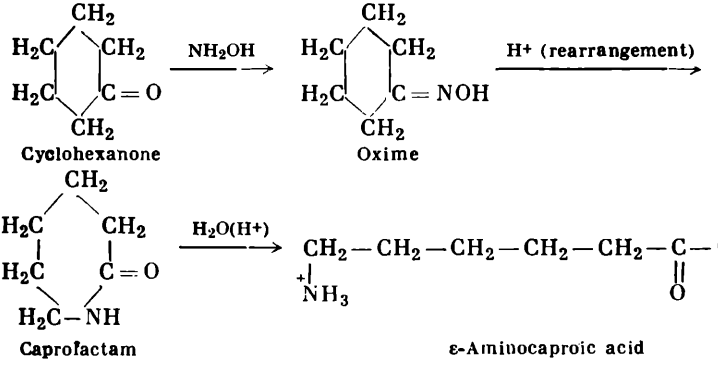
2. ω-Amino acids can be synthesized by either of the following two methods.

(a) A number of tetrachloroalkanes are obtained by the telomerization of ethylene with carbon tetrachloride (A. N. Nesmeyanov, R. Kh. Freidlina and coworkers), which are then readily converted into ω-amino acids:

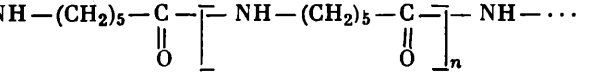
$$n CH_2=CH_2+CCl_4 \longrightarrow Cl-(CH_2CH_2)_n-CCl_3 \xrightarrow[-HCl]{H_2O(H_2SO_4)}$$

$$\longrightarrow Cl-(CH_2CH_2)_n-\underset{\underset{O}{\|}}{C}-OH \xrightarrow[-NH_4Cl]{3NH_3} NH_2-(CH_2CH_2)_n-\underset{\underset{O}{\|}}{C}-O^-\overset{+}{N}H_4$$

(b) The Beckmann rearrangement (see Volume III) of the oximes of cyclic ketones. Of the greatest practical importance is the rearrangement of the oxime of cyclohexanone:



The caprolactam thus obtained polymerizes into high-molecular-weight polycapramide:

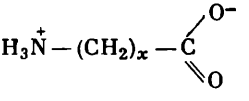


from which capron fibre is made.

B. Properties of Amino Acids

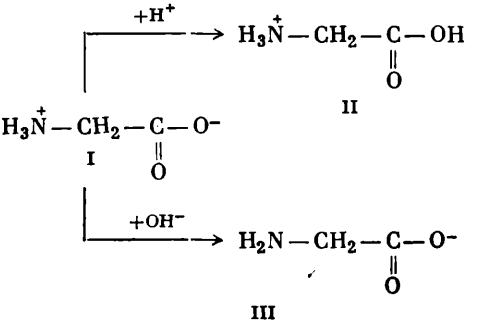
The names, formulas and properties of the most important amino acids are listed in Table 4.11.

As has already been said, all amino acids are in fact inner salts of the type



and this is reflected in their physical properties: they are high-melting, nonvolatile, insoluble in hydrocarbons and ether and most of them are soluble in water.

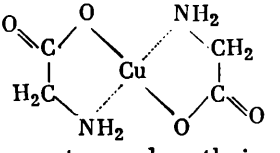
1. The reactions of amino acids with acids and alkalis are exemplified by the case of aminoacetic acid:



In the first case there is formed the cation II of a salt of the amino acid as a base, in the second, the anion III of a salt of the amino acid as an acid, and only at a strictly definite (for each amino acid) hydrogen ion concentration of the solution (the isoelectric point) does there exist the inner salt I. On electrolysis of such a solution the amino acid migrates neither to the cathode nor to the anode. In more acidic solutions, amino acids subjected to electrolysis move in the form of cation II to the cathode, while in less acidic solutions they move in the form of anion III to the anode.

α-Amino acids form characteristic copper inner-complex salts, the structure of which is exemplified by the structure of the copper

salt of aminoacetic acid:



2. Amino acids form esters when their alcoholic solutions are acted on by hydrogen chloride. This results, of course, in the formation of ester hydrochlorides, from which free esters can be obtained by removing hydrogen chloride with the aid of silver oxide, lead oxide or triethylamine:

$$\overset{+}{N}H_3-CH_2-\underset{\underset{O}{\|}}{C}-O^- + C_2H_5OH + HCl \longrightarrow \left[\overset{+}{N}H_3-CH_2-\underset{\underset{O}{\|}}{C}-OC_2H_5\right]Cl^-$$

$$2\left[\overset{+}{N}H_3-CH_2-\underset{\underset{O}{\|}}{C}-OC_2H_5\right]Cl^- + Ag_2O \longrightarrow$$

$$\longrightarrow NH_2-CH_2-\underset{\underset{O}{\|}}{C}-OC_2H_5 + 2AgCl + H_2O$$

The esters of ordinary amino acids are liquids which can be distilled out *in vacuo*. It is exactly by means of the esterification of the sum of amino acids resulting from the hydrolysis of proteins and by the vacuum distillation and subsequent hydrolysis that Emil Fischer succeeded in isolating individual amino acids and developed a method of establishing the amino-acid composition of proteins.

3. The action of phosphorus pentachloride on amino acids gives the hydrochlorides of the acid chlorides of amino acids, which are rather unstable compounds and on elimination of HCl form quite unstable free acid chlorides:

$$\overset{+}{N}H_3-CH_2-\underset{\underset{O}{\|}}{C}-O^- + PCl_5 \longrightarrow \left[\overset{+}{N}H_3-CH_2-\underset{\underset{O}{\|}}{C}-Cl\right]Cl^- + POCl_3$$

4. Amino acids are acylated at the amino group:

$$\overset{+}{N}H_3-CH_2-\underset{\underset{O}{\|}}{C}-O^- + \left(CH_3-\underset{\underset{O}{\|}}{C}\right)_2O \longrightarrow$$

$$\longrightarrow CH_3-\underset{\underset{O}{\|}}{C}-NH-CH_2-\underset{\underset{O}{\|}}{C}-OH + CH_3-\underset{\underset{O}{\|}}{C}-OH$$

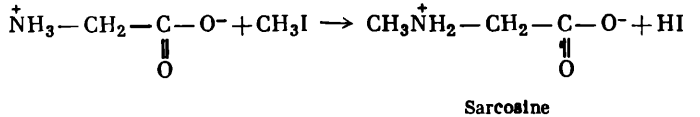
Acetylglycine

$$\overset{+}{N}H_3-CH_2-\underset{\underset{O}{\|}}{C}-O^- + C_6H_5-\underset{\underset{O}{\|}}{C}-Cl \longrightarrow C_6H_5-\underset{\underset{O}{\|}}{C}-NH-CH_2-\underset{\underset{O}{\|}}{C}-OH + HCl$$

Benzoylglycine
(hippuric acid)

Hippuric acid formed in the last reaction is a substance which is excreted in small quantities in the urine of mammals as a means of elimination of the toxic benzoic acid which has found its way into the organism together with food.

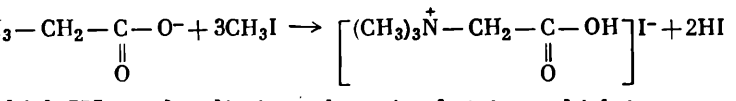
5. Amino acids may also be alkylated at the amino group. The alkylation of glycine yields methylaminoacetic acid called **sarcosine** (*methylglycine*):



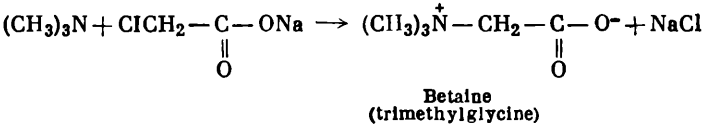
Sarcosine

which is contained in the combined state in certain proteins.

With an excess of methyl iodide there is obtained the quaternaryammonium-substituted acetic acid:

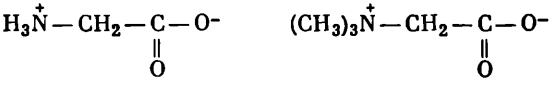


from which HI can be eliminated to give **betaine**, which is more conveniently synthesized by the action of trimethylamine on chloroacetic acid:



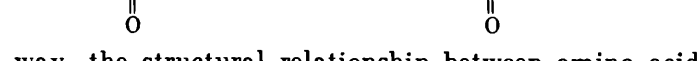
Betaine
(trimethylglycine)

Betaine is the name derived from the sugar-beet (*Beta vulgaris*), in the juice of which it occurs; the general name **betaines** is now extended to a series of inner salts in which the anion and cation are bound within a single molecule. In this sense, one speaks of the betaine-like structure of amino acids:



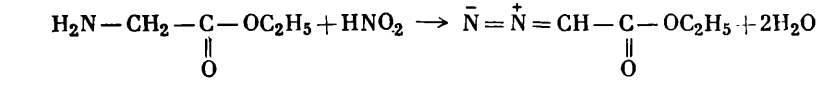
Betaines possess a high dipole moment and have salt-like properties (they are solid, nonvolatile, and water-soluble).

6. Nitrous acid reacts with primary amino acids in the same manner as with aliphatic primary amines: nitrogen is evolved and the amino group is replaced by a carbonyl group (the Van Slyke method):



In this way, the structural relationship between amino acids and the corresponding hydroxy acids can be established.

All the preceding reactions are common to all amino acids, regardless of the position of the amino group. The reaction between nitrous acid and the esters of α-amino acids takes a different course:

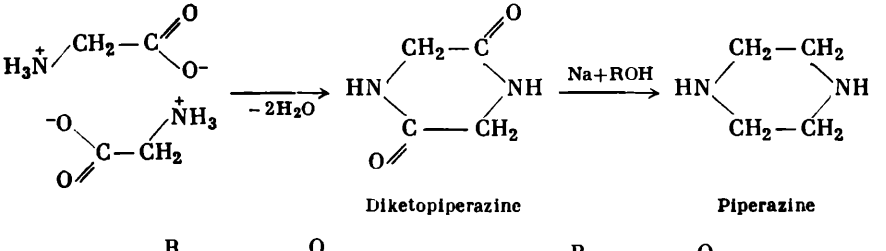


This reaction gives an ester of an α-diazo acid, which belongs to the important type of class of aliphatic diazo compounds (see Volume I, page 294).

All other types of esters of amino acids (β-, γ-, etc.) react with nitrous acid in the same way as the amino acids themselves—with the replacement of the NH_2 group by OH.

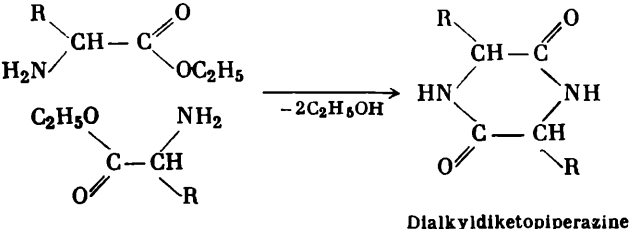
7. Especially interesting are the reactions of self-acylation of amino acids. They proceed differently, depending on the type of amino acids.

Many of the α-amino acids even on mild heating lose 2 molecules of water to form cyclic substituted amides, often called cyclic anhydrides or **diketopiperazines.** In the case of other α-amino acids, one has to heat their esters which undergo cyclization reactions more readily by loss of two molecules of alcohol:



Diketopiperazine

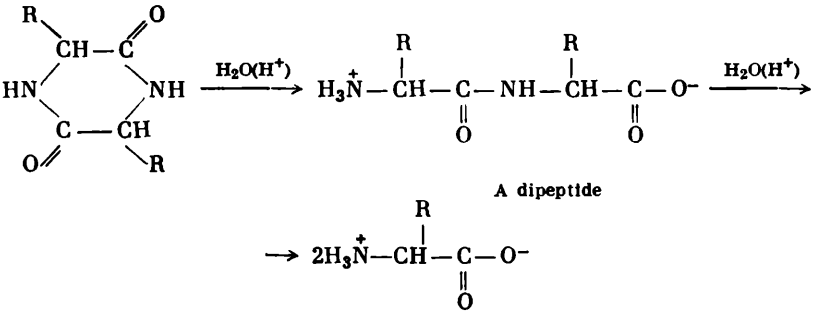
Piperazine



Dialkyldiketopiperazine
(R=alkyl)

Diketopiperazines are neutral crystalline compounds with rather high melting points, which are soluble in hot water and in alcohol. When acted on by aqueous acids (and alkalis) they, like amides, are first hydrolysed partially, with the opening of the ring, to **dipepti-**

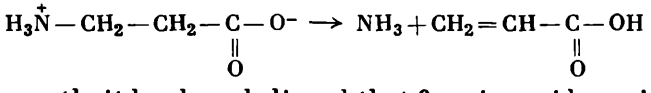
des, and then converted into two molecules of an amino acid:



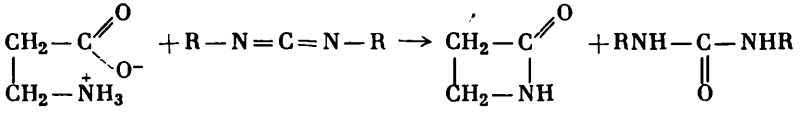
On heating dipeptides become capable of recyclization into diketopiperazines.

It is easy to see that diketopiperazines are the nitrogen analogues of lactides obtained from α-hydroxy acids (see page 62). α-Amino acids are the only amino acids whose two molecules combine to form amides with a six-membered heterocyclic ring.

β-Amino acids when acted on by acids or heated readily part with ammonia (just as β-hydroxy acids lose the elements of water under these conditions) to yield α,β-unsaturated acids:

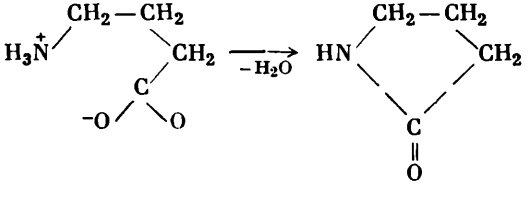


Until recently it has been believed that β-amino acids are incapable of forming inner amides. It has been found, however, that they give rise to **lactams** under the influence of dicyclohexylcarbodiimide, R—N=C=N—R (where R = cyclohexyl, C_6H_{11}), which is a strong dehydrating agent:



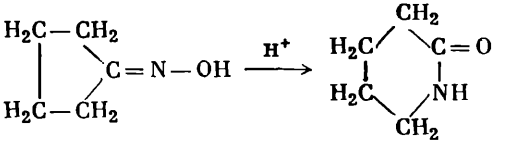
These unusual β-lactams are labile compounds and are easily decyclized on hydrolysis. The β-lactam structure has been found, for example, in penicillin (see Volume IV).

γ-Amino acids are very easily converted by loss of water into lactams



which is in accord with the usually high stability of five-membered rings. γ-Lactams undergo decyclization on both acid and alkali hydrolysis to form γ-amino acids (or their salts), though they do so more difficultly than β-lactams.

The higher lactams are also capable of existence. They are more simply obtained (in excellent yield) by the Beckmann rearrangement of the oximes of cyclic ketones (page 166):

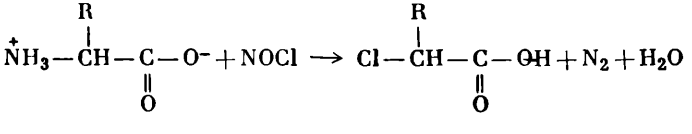


8. Apart from cyclic amides (diketopiperazines and lactams), all amino acids are capable of forming the above-mentioned acyclic amides—dipeptides—by way of acylation of the amino group of one acid by the carboxyl group of another acid. These important compounds will be treated after the discussion of the elucidation of the structure and configuration of amino acids, which will supplement the information regarding the reactions of amino acids.

C. Elucidation of the Structure of Natural Amino Acids

Many of the simplest amino acids were known since the twenties of the last century. As early as 1820 Henri Braconnot (1781-1855), by boiling glue with dilute sulphuric acid, isolated glycocoll (glycine) from the hydrolysis products of proteins.

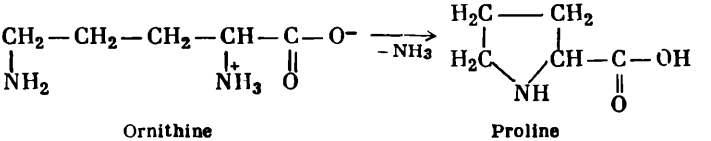
That natural amino acids belong to the class of α-amino acids can easily be deduced from their ability to form diketopiperazines and from their characteristic inner-complex copper salts. Nitrous acid converts them into α-hydroxy acids, many of which were known as early as the second half of the 18th century. If an unknown hydroxy acid is obtained, the amino group can be replaced by chlorine in the presence of nitrosyl chloride



and then, by substituting hydrogen for chlorine under the action of zinc, a known carboxylic acid can be produced (or a dibasic acid in the case of aminodicarboxylic acids). In this way, for example, isovaleric acid can be prepared from valine, isocaproic acid from leucine, and glutaric acid from glutamic acid, all of which can be

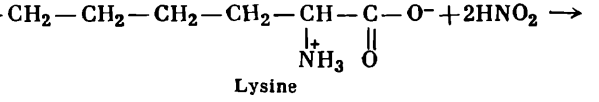
easily identified by the formation of any solid derivatives (for example, anilides, see Volume IV).

In the case of diamino acids, one has also to establish the position of the second amino group, which can be achieved in certain cases by making use of the facile cyclization of the acids in the presence of ammonia-removing substances:

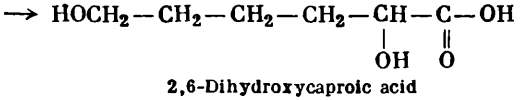


Ornithine Proline

It is also possible to replace both amino groups by hydroxyl groups by the action of nitrous acid



Lysine

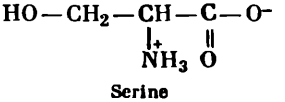


2,6-Dihydroxycaproic acid

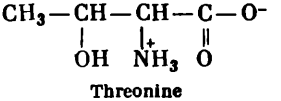
and make certain that one hydroxyl group, say, a primary hydroxyl group, forms on oxidation an aldehyde and not a keto function.

In case there is a third functional group, in addition to the amino and carboxyl groups (in fact, the following groups may be present: HO—, HS—, CH_3S—, or —S—S—), it is necessary to establish the structure of the carbon skeleton. This is accomplished by means of the reduction, under specified conditions, of the groups SH and —S—S—, which on hydration over nickel are removed as hydrogen sulphide (as methyl mercaptan in the case of the CH_3S group) and are replaced by hydrogen. The replacement of hydroxyl by hydrogen has already been considered.

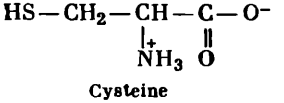
The place of the second functional group can be located by the reactions given below. In doing this, it is necessary to remember that we are dealing here with the four amino acids found in proteins, each of which has three different functional groups:



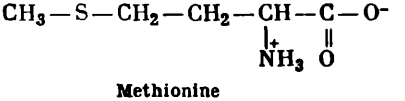
Serine



Threonine

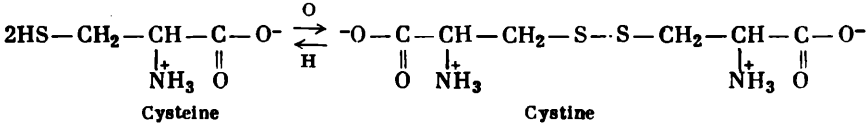


Cysteine



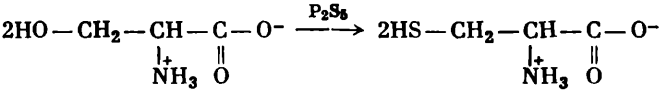
Methionine

Cystine is left out since its structure can be determined by its facile interconversion with cysteine:



Cysteine Cystine

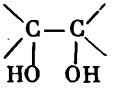
The close relationship between cysteine and serine is established by the conversion of serine into cysteine by the action of P_2S_5:



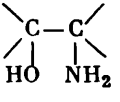
Serine Cysteine

The β-position of the hydroxyl group in serine can be established by the conversion of serine under the action of nitrous acid into glyceric acid (the replacement of an α-amino group by an OH group).

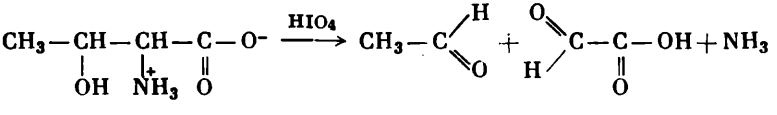
The structure of threonine is elucidated by its oxidation with periodic acid, which breaks not only the linkages



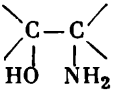
but also the linkages



On periodate oxidation threonine turns into acetaldehyde, glyoxalic acid and ammonia:

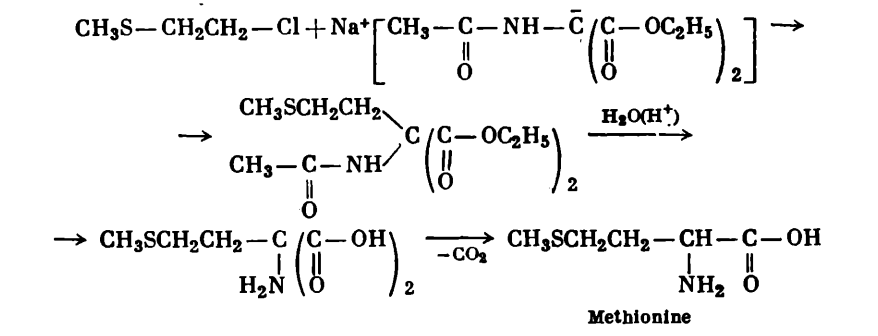


from which it follows that threonine has a terminal methyl group and the grouping



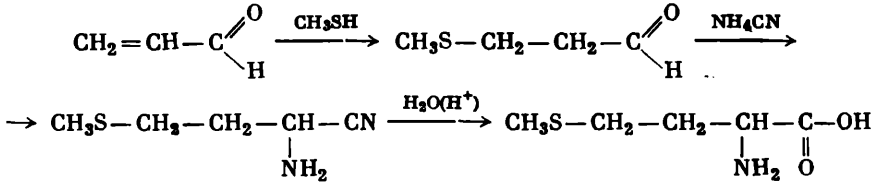
All the inferences concerning the structure of amino acids are supported, as is always the case, by their synthesis. As an illustration, the structure of methionine follows from its synthesis by alkylation of the sodium derivative of acetylaminomalonic ester (page 164)

by the action of $CH_3S-CH_2CH_2-Cl$:

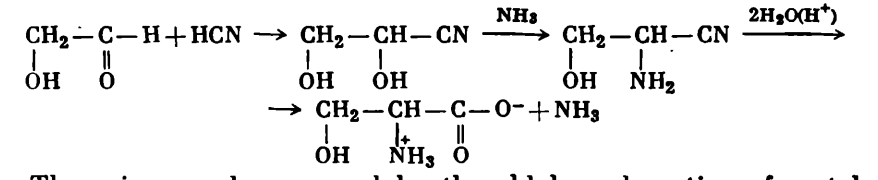


Methionine

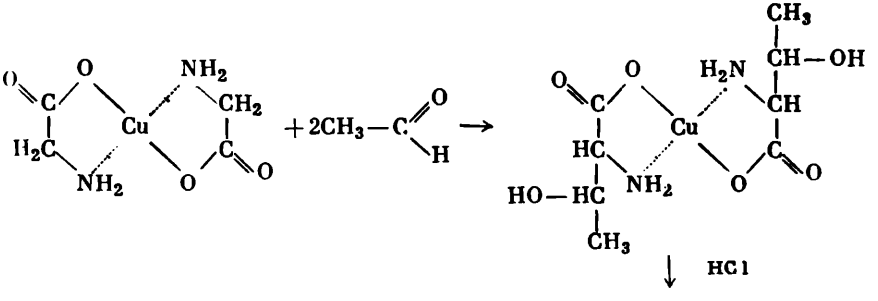
and is confirmed by the synthesis from propylene via acrolein (an industrial method):

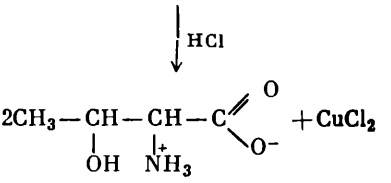


Serine was prepared (E. Fischer and H. Leuchs) by the Strecker synthesis from glycolaldehyde:



Threonine can be prepared by the aldol condensation of acetaldehyde with a copper salt of glycine (Akabori). The cupric ion linked to the amino group not only protects the amino group but also ionizes the hydrogens of the α-methylenic linkage (since the nitrogen in the copper complex assumes the ammonium state, $Cu-\overset{+}{N}H_2-$):

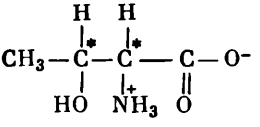




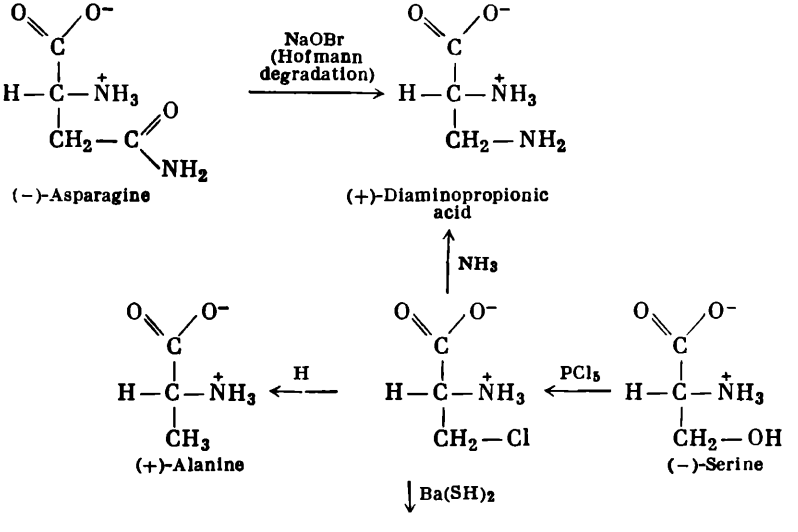
Further reactions of synthesis and interconversion of α-amino acids will be described in the following section.

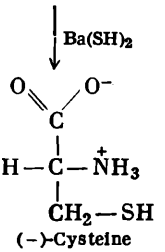
D. The Configuration of Natural α-Amino Acids

All α-amino acids (except glycine, $H_2N—CH_2COOH$) possess an asymmetric carbon atom (namely, an alpha-carbon atom); some of them have two asymmetric carbon atoms, say, threonine:



The configuration of the α-asymmetric carbon atom is the same for all natural α-amino acids but one (glycine). This has been proved by the interconversion of natural α-amino acids by means of reactions which neither break nor create bonds to the asymmetric carbon atom (they are said to leave the asymmetric carbon atom intact) and, consequently, are unexceptionable from the stereochemical point of view (see page 50 concerning Walden inversion). The following are examples of such reactions:





(−)-Cysteine

All these amino acids, which rotate the plane of polarization of light in different directions, naturally belong either to the D- or to the L-series. It remains to find out which of the series they belong to, for which purpose it is necessary to trace their spatial relationship to D- or L-glyceraldehyde or to L-tartaric acid, or else to one of the hydroxy acids whose relations (page 38) with these reference compounds have already been established. This has been done by W. Kuhn and K. Freudenberg who rather convincingly compared the molecular rotations of the plane of polarized light for a number of the derivatives of D- and L-lactic acids, on the one hand, and (+)-alanine, on the other (Table 4.12).

TABLE 4.12. **Comparison of the Molecular Rotations [M]D of Analogous Derivatives of D- and L-Lactic Acids and Natural Alanine**

R	X	Derivatives of lactic acids $CH_3-CH(OR)-C(=O)-X$		Derivatives of natural (+)-alanine $CH_3-CH(NHR)-C(=O)-X$
		(+)-L-	(−)-D-	
I	II	III	IV	V
C_6H_5CO	NH_2	+120°	−120°	+70-80°
C_6H_5CO	OC_2H_5	+49°	−49°	+12°
C_6H_5CO	OCH_3	+35°	−35°	0°
CH_3CO	OC_2H_5	+76°	−76°	−74°
n-$CH_3C_6H_4SO_2$	OC_2H_5	−129°	+129°	−78°

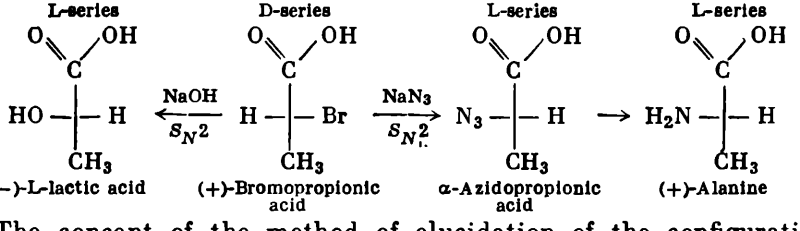
The derivatives compared have the following structures:

$$CH_3-\underset{\displaystyle RO}{\underset{|}{CH}}-\overset{\displaystyle O}{\overset{\|}{C}}-X \quad \text{and} \quad CH_3-\underset{\displaystyle RHN}{\underset{|}{CH}}-\overset{\displaystyle O}{\overset{\|}{C}}-X$$

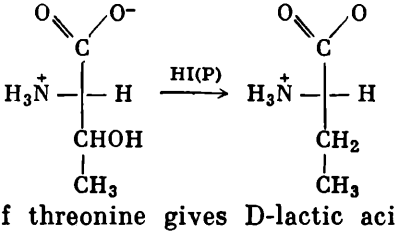
Since the structures of lactic acid and alanine are analogous, it is natural to expect that molecular rotation varies identically in going from one analogous derivative to another in the case of iden-

tical configuration. A comparison of the columns III and V in the table shows that the variation of $[M]_D$ is the same, and a comparison of columns IV and V establishes the difference. It follows that natural (+)-alanine corresponds to L-lactic acid in configuration and, hence, to L-tartaric acid and L-glyceraldehyde (page 38). Thus, all natural amino acids belong to the L-series.

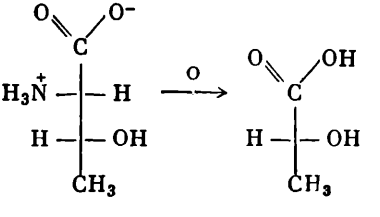
This highly probable conclusion becomes reliable if one takes into account the considerations based on the knowledge of the laws of Walden inversion (page 50). If the rate of nucleophilic substitution corresponds to a second-order reaction (S_N2), i.e., if the rate is proportional to the product of the concentrations of both reagents, then, as has been found by Ingold, Hughes and coworkers, the reaction involves a Walden inversion. This regularity enabled these English scientists to establish, independently, the identity of the configurations of (+)-alanine and (+)-L-lactic acid:



The concept of the method of elucidation of the configuration of the second asymmetric carbon atom, if there is one, may be illustrated by considering threonine as an example. As is always the case with natural α-amino acids, the α-carbon atom of threonine has the L-configuration. This follows from the fact that threonine is reduced by hydrogen iodide in the presence of red phosphorus to L-aminobutyric acid (the reaction leaves the asymmetric carbon atom intact):

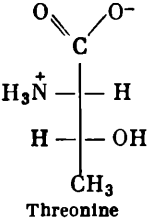


The oxidation of threonine gives D-lactic acid:

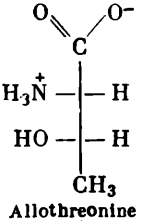


from which one can deduce the D-configuration of the β-carbon atom. The diastereomer of threonine is called **allothreonine***. The above-described synthesis of threonine by the condensation of acetaldehyde with a copper salt of glycine gives both diastereomers.

Threonine corresponds in configuration to L-threose (the *threo*-configuration), while allothreonine has the same configuration as L-erythrose (the *erythro*-configuration) (see Table 4.8):



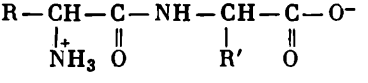
Threonine
(*threo*-configuration)



Allothreonine
(*erythro*-configuration)

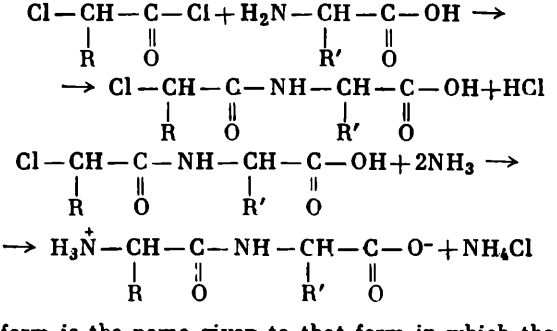
4.7. Dipeptides and Polypeptides

Dipeptides are α-amino-N-acylamino acids



Polypeptides are built up, according to the same amide principle, of several identical or different amino acids. They are named according to the number of amino-acid residues involved: di-, tri-, and other polypeptides.

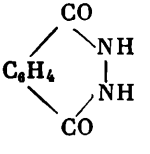
Dipeptides with identical α-amino-acid residues can be prepared by the hydrolytic cleavage of diketopiperazines (page 170). Dipeptides with any α-amino-acid residues were obtained by E. Fischer by the acylation of an amino acid at the amino group by an acid chloride of an α-halogen-substituted acid with subsequent replacement of the α-halogen by an amino group under the action of ammonia:



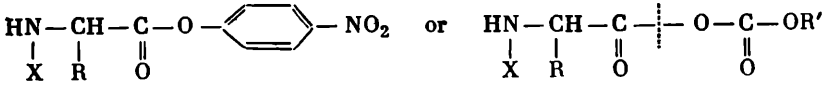
* The *allo*-form is the name given to that form in which the configuration of the second asymmetric carbon atom is inverted.—*Tr.*

The same sequence of reactions when applied to the dipeptide obtained will lead to a tripeptide, etc. Emil Fischer synthesized in this way an **octadecapeptide** consisting of 18 amino-acid residues.

In newer methods of synthesis of polypeptides the starting materials are the acid chlorides of amino acids (or other functional derivatives of amino acids possessing a sharply pronounced acylating power) with a protected amino group. Such a protection is required in order to prevent the acid chloride of the first amino acid from acylating a molecule like itself and to make it condense with the second amino acid. The protection of the amino group by acetylation is inconvenient since the conditions for removal of the acetyl group by hydrolysis are such that the di- or polypeptide will itself be hydrolysed and broken down into the component amino acids. Therefore, the amino group of the acid which is to be used as an acylating agent and which is converted into an acid chloride for this purpose is protected by introducing into the amino group such a grouping which would be easy to remove from the dipeptide by hydrolysis under very mild conditions or by any other procedure. For instance, the group CF_3CO- can be removed by treatment with a weak alkali or by hydrogenolysis; the grouping $C_6H_5CH_2OCO-$ can be easily removed by hydrogenation over a palladium catalyst, by reduction with a solution of sodium in liquid ammonia or by the action of hydrazine; under the action of hydrazine the phthalyl group is split off as



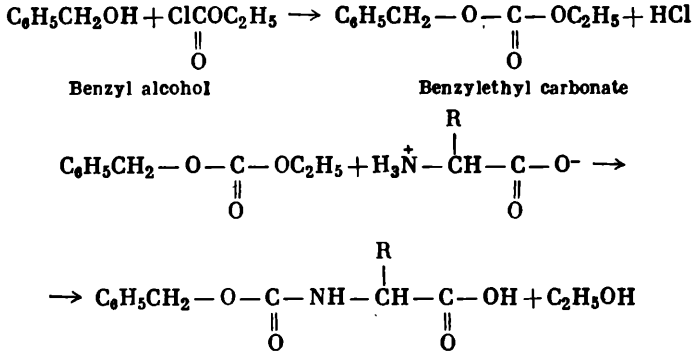
As to the question of the functional derivative in the form of which the carboxyl group of the protected amino acid must be, readily acylating esters or mixed anhydrides are used more often than acid chlorides; for example,



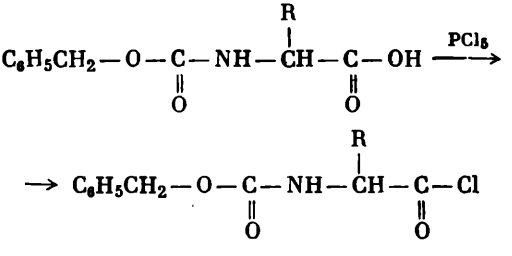
where X is the protecting group, and R′ is the residue of the sterically hindered aliphatic alcohol, say, $(CH_3)_2CH—CH_2OH$, which brings about the cleavage of the acylating molecule along the dotted line.

Let us cite some examples of protection of the amino group and acylation of one amino acid (in the form of various functional derivatives) by another with the subsequent removal of the protecting group from the dipeptide.

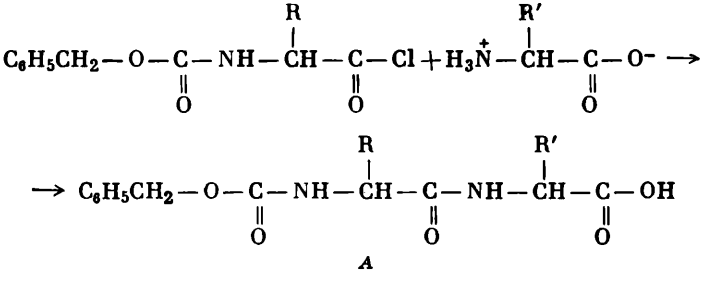
Example 1. (a) Protection of the amino group:



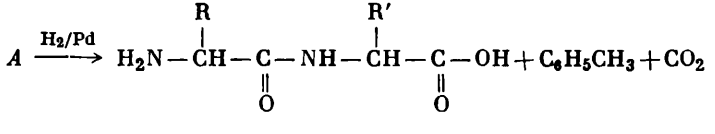
(b) Conversion of the carboxyl group of the protected amino acid into a reactive functional derivative (into an acid chloride in this particular case):



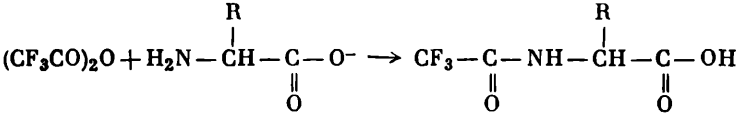
(c) Coupling into a dipeptide:



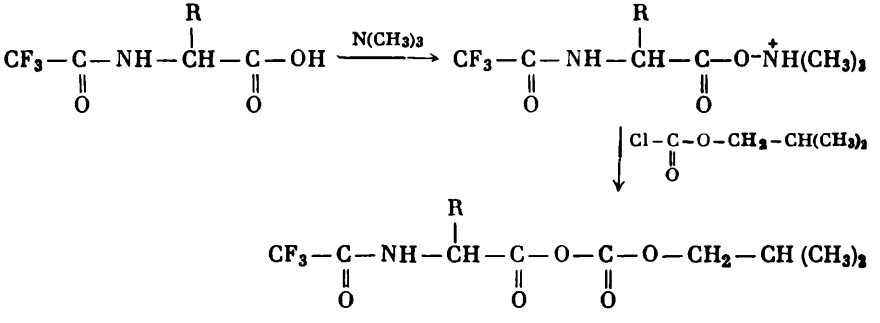
(d) Removal of the protective group (E. Bergmann):



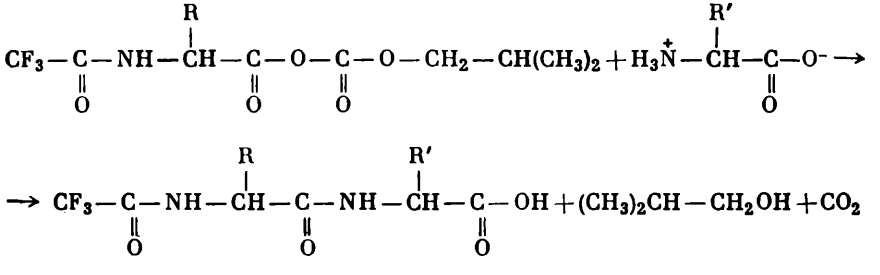
Example 2. (a) Protection of the amino group:



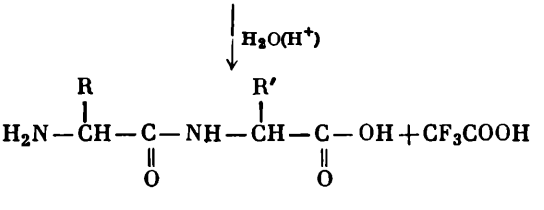
(b) Conversion into some reactive functional derivative (a mixed anhydride)*:



(c) Coupling into a dipeptide:

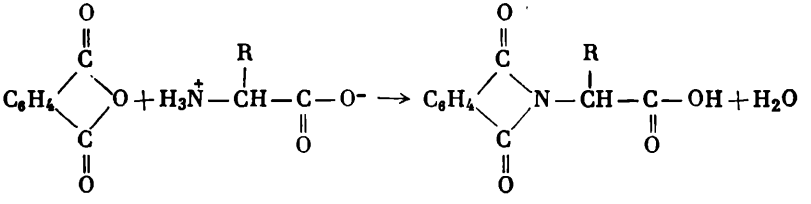


(d) Removal of the protecting group (Weygand, Wieland):

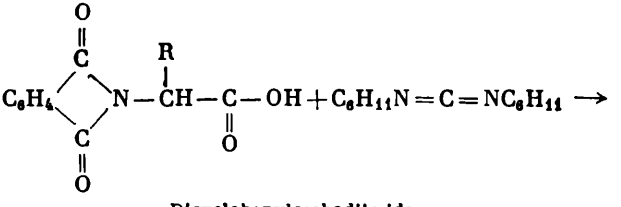


* Isobutyl chlorocarbonate is taken since it is not hydrolysed across the C—$OCH_2CH(CH_3)_2$ linkage because of steric hindrances.

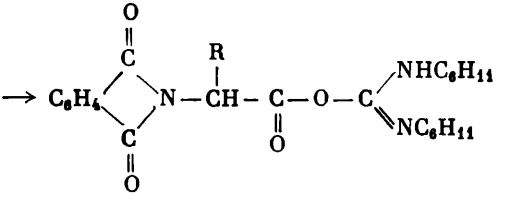
Example 3. (a) Protection of the amino group (the formation of a phthaloyl derivative):



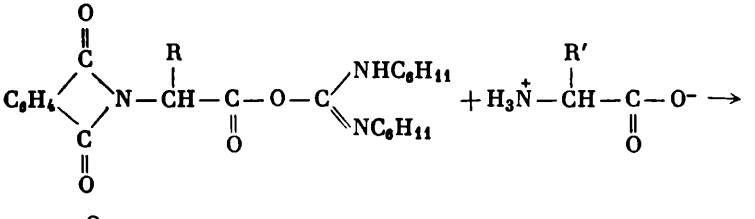
(b) Conversion into a reactive acyl derivative of dicyclohexylisourea:

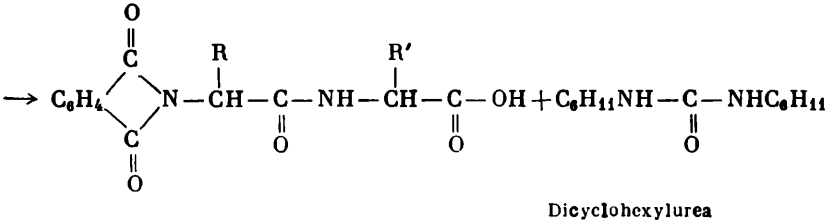


Dicyclohexylcarbodiimide



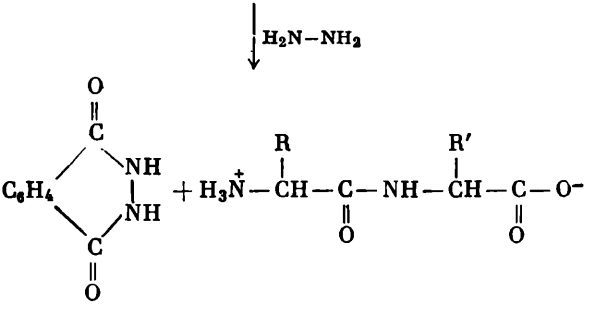
(c) Coupling into a dipeptide:





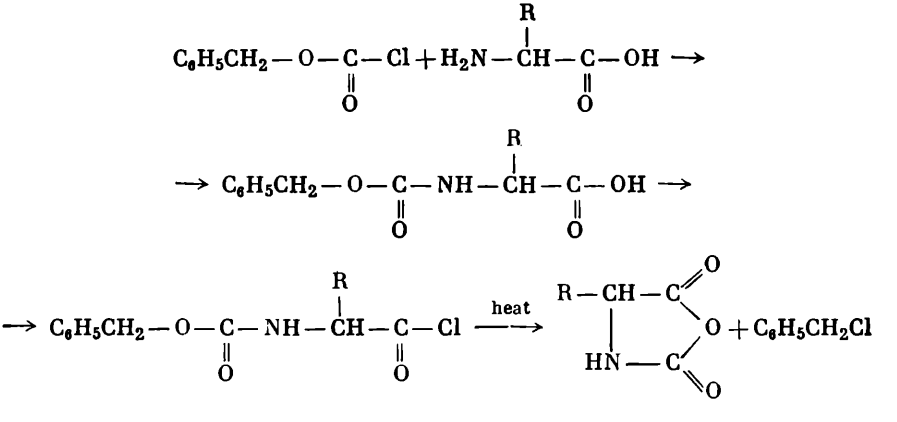
Dicyclohexylurea

(d) Removal of the protecting group (Sheehan):



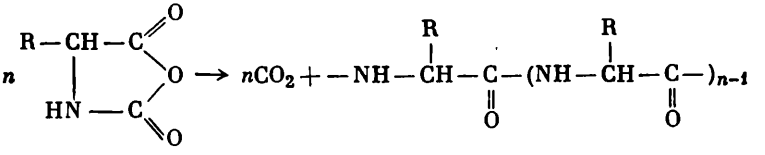
The same methods (and a number of others which are not considered here) are also applicable for the synthesis of tri-, tetra- and other polypeptides. Some concrete examples of natural polypeptides and their synthesis will be discussed in Chapter 23 devoted to proteins (see Volume IV). Such a directed synthesis of a polypeptide with a definite sequence of several tens of amino-acid residues is an extremely tedious and time-consuming procedure and would have been practically impossible without the use of modern methods of synthesis and separation of substances (see Chapter 23, Volume IV).

Quite different is the preparation of polypeptides, even those with a high molecular weight, from one type of amino-acid residues. A special method has been worked out (Leuchs) for this purpose. This may be exemplified by glycine (R=H):

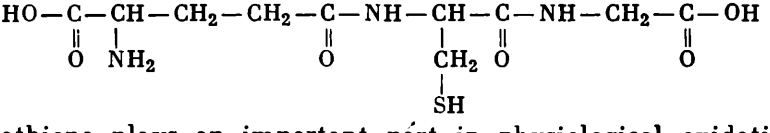


Such cyclic internal mixed anhydrides when heated break down with the evolution of carbon dioxide and the formation of high-

molecular-weight polypeptides:



Polypeptides, like the amino acids themselves, are amphoteric and each polypeptide has an isoelectric point of its own. Polypeptides are compounds which are intermediate between amino acids and proteins: under the conditions of acid and alkaline hydrolysis polypeptides and proteins decompose into amino acids. Lower polypeptides are crystalline substances soluble in water; in going to higher-molecular-weight polypeptides the ability to crystallize falls off. Polypeptides may also contain monoaminodicarboxylic acids, such as aspartic and glutamic acids, in which case they assume acidic properties due to the second carboxyl group. Polypeptides formed with the participation of diamino acids have basic character. The properties of polypeptides formed with the participation of serine (β-hydroxy-α-aminopropionic acid) and cysteine (β-mercapto-α-aminopropionic acid) reflect the presence of an OH and a SH group, respectively. Certain polypeptides play an important biological part in living organisms. Such is, for example, the tripeptide **glutathione** which is built up of three amino acids—glycine, glutamic acid and cysteine:

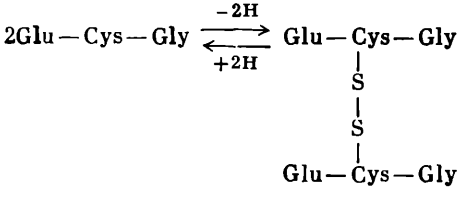


Glutathione plays an important part in physiological oxidation-reduction processes.

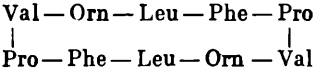
In the chemistry of proteins and polypeptides, the formulas are written with the names of amino-acid residues designated in abbreviated form (see Table 4.11). For example, Glu stands for glutamic acid, Cys for cysteine, Gly for glycine. The shortened formula of glutathione will be as follows:

Glu—Cys—Gly

Like all mercaptans, glutathione is readily oxidized to the disulphide form and is readily reformed from the latter by reduction:

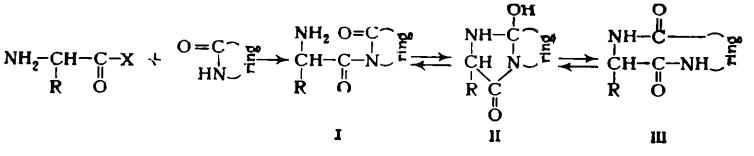


Polypeptides may also have a macrocyclic structure. An example is gramicidin (an antibiotic)



Here Val stands for valine, Orn for ornithine, Leu for leucine, Phe for phenylalanine, and Pro for proline.

How are new amino-acid units introduced into the ring and, hence, how does the extension of a cyclic polypeptide proceed? The answer to this question has been given by the experiments conducted by M. M. Shemyakin who showed that the acylation of the amide grouping of the polypeptide ring by an amino acid (of course, by one of its amino-acylating forms) involves the following series of reactions:



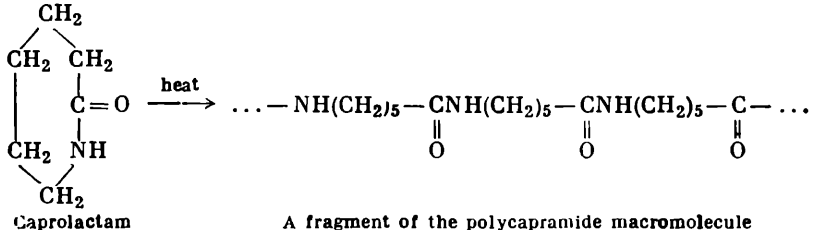
I II III

Thus, the amino acid is found to be incorporated into the ring at the stage III.

A number of relatively complex polypeptides (or, what is the same thing, simple proteins) play the role of hormones and enzymes in the organism. They will be discussed together with proteins (see Volume IV).

4.8. Polyamides Derived from ω-Amino Acids

Analogues (though remote) of polypeptides can be obtained synthetically from ω-amino acids. Compounds of this type, beginning with the "polypeptide" of ω-aminocaproic acid, have found practical application. These polypeptides (or polyamides, as they are called) are prepared by heating cyclic lactams formed by the Beckmann rearrangement of oximes of cyclic ketones (see, for example, page 166):

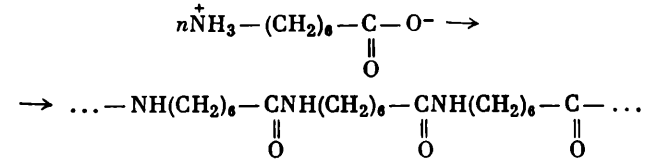


Caprolactam

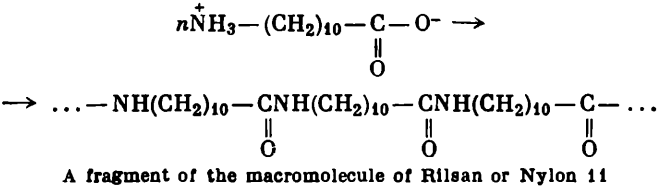
A fragment of the polycapramide macromolecule (Nylon 6 or Capron)

The melt of this polymer (m. p. 215-220°C) can be spun directly into fibres (Nylon 6 produced in this country under the name of Capron). This method can, in principle, be used to prepare homologues of Nylon 6.

Polyamides can also be prepared by the polycondensation of amino acids themselves (with elimination of water):



A fragment of the macromolecule of Enant or Nylon 7

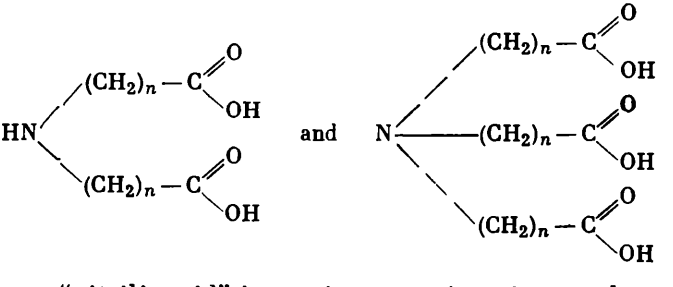


A fragment of the macromolecule of Rilsan or Nylon 11

Polyamides of the types indicated are used to produce synthetic fibres, artificial fur, leather substitutes and plastic articles, which possess high strength and elasticity (of the ivory type). Nylon 6 has found the widest application because of the availability of the raw material and the long-elaborated synthesis route. Nylon 7 (produced in the USSR under the name of Enant) and Nylon 11 (Rilsan) are noted for high strength and lightness.

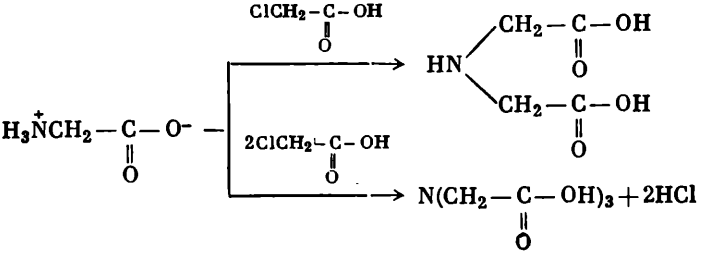
4.9. Imino and Nitrilic Acids

Imino and nitrilic acids are compounds of the following types:

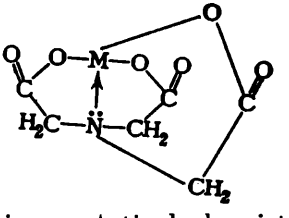


The name "nitrilic acid" is a misnomer since it may be confused with nitriles. With $n = 1$ the formulas written above represent α-iminodiacetic and α-nitrilotriacetic acids. Imino acids are ob-

tained as by-products in the synthesis of amino acids by the action of ammonia on halogen-substituted acids, especially in the absence of a large excess of ammonia. Both these acids can be prepared by treating glycine with monochloroacetic acid:

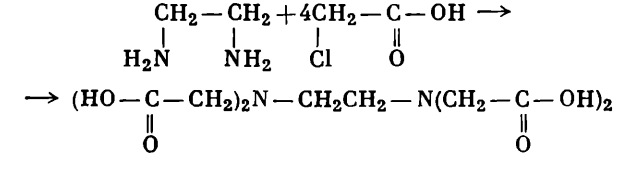


Nitrilotriacetic acid (abbreviated to NTA) forms complex salts with many metals (these salts are called **complexones**):



and finds application in analytical chemistry and in engineering for separation of metals because many salts of this type are soluble in organic solvents and are extracted by them from aqueous solution. Nitrilotriacetic acid is widely used as a sequestering agent to eliminate the "hardness" of water (by binding calcium into a soluble complex).

Ethylenediaminetetraacetic acid (EDTA) is also used for the same purpose. This acid is obtained by the action of monochloroacetic acid on ethylenediamine:



4.10. Aminoaldehydes and Aminoketones

In contrast to amino acids, aminoaldehydes and aminoketones do not occur in natural compounds and have not found wide practical application. We shall therefore confine ourselves to a brief consideration of these compounds.

α-Aminoaldehydes are very unstable. They are used in syntheses in the form of acetals obtained from the acetals of α-chloroaldehydes:

$$ClCH_2-CH(OC_2H_5)_2+2NH_3 \longrightarrow NH_2CH_2-CH(OC_2H_5)_2+NH_4Cl$$

α-Aminoketones are more stable. They are prepared from chlorine-substituted ketones:

$$ClCH_2-\underset{\underset{O}{\|}}{C}-CH_3+2NH_3 \longrightarrow NH_2CH_2-\underset{\underset{O}{\|}}{C}-CH_3+NH_4Cl$$

β-Aminoaldehydes and β-aminoketones are prepared by the addition of ammonia to unsaturated carbonyl compounds:

$$\begin{matrix}CH_3\\ \\ CH_3\end{matrix}\!\!>\!C=CH-\underset{\underset{O}{\|}}{C}-CH_3+NH_3 \longrightarrow \begin{matrix}CH_3\\ \\ CH_3\end{matrix}\!\!>\!\underset{\underset{NH_2}{|}}{C}-CH_2-\underset{\underset{O}{\|}}{C}-CH_3$$

As is always the case, the orienting effect of the carboxyl group is such that hydrogen adds on to the double bond in the neighbouring position, and the amino group in the β-position (contrary to Markovnikov's rule).

The reaction between formaldehyde and ketones containing a free CH_2 α-linkage in the presence of an amine $R_2'NH$ may be used to prepare a β-aminoketone (Mannich reaction):

$$R-CH_2-\underset{\underset{O}{\|}}{C}-R'+CH_2O+HNR_2' \longrightarrow R-\underset{\underset{CH_2-NR_2'}{|}}{CH}-\overset{\overset{O}{\|}}{C}-R'$$

The reaction proceeds via the intermediate stage of formation of an unsaturated ketone.

XIX. Steric Hindrances and Conformational Analysis

(A) Conformational Analysis

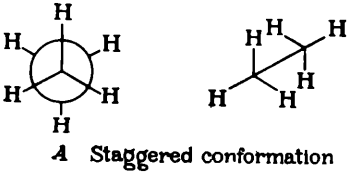
The rotation about a double bond is impossible without disturbing the π-bond, which requires a large amount of energy (about 60 kcal/mole). This is responsible for the *cis-trans* isomerism of olefins and their derivatives.

The rotation about a single bond had long been considered to be completely free. Only in 1936 was it suggested and substantiated that this rotation is hindered, the amount of rotation being different for different saturated compounds (Kemp and Pitzer). Calculations

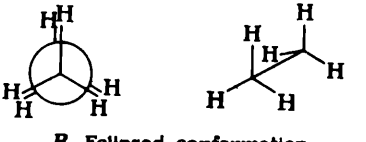
of the thermodynamic properties of hydrocarbon molecules, in which all the possible vibrations and rotations of atoms in a molecule were taken into account, led to results differing noticeably from the experimental data. Kemp and Pitzer showed that these deviations are reduced to a minimum if the assumption of free rotation is ignored and models with a sinusoidal potential energy barrier to rotation are applied in the calculations (the meaning of the potential energy barrier will be disclosed later in the text).

When two nonbonded atoms come closer together and are at a distance only slightly less than the sum of their van der Waals radii, a steric repulsion occurs, i.e.,.repulsion between the electron shells of these atoms, which is sharply increased upon their further approach. Thus, when estimating the energy of a molecule and its reactivity one should take into account not only the bond energy, polar effects, etc., but also the steric interaction between non-bonded atoms. When a bond is being formed between two carbon atoms, the distance between them becomes less than the sum of their van der Waals radii. As a result, the groups linked to these atoms approach each other in space as well and even if they are not large, a steric interaction between them is possible (the bond lengths are always considerably smaller than the sum of the van der Waals radii of the corresponding atoms).

Consider, as an example, the ethane molecule. As one methyl group is rotated with respect to the other, the molecule assumes one of the forms given below or one of the intermediate forms. The Newman projection formulas are given on the left (the ethane molecule is viewed from the top straight down the C—C bond; the top carbon atom is designated as a dot and the bottom carbon as a circle). In the model *B* the hydrogens on the rear carbon atom are directly behind those on the front carbon (although in the drawing they are offset a little for clarity). With the sawhorse drawings shown on the left, the molecule is viewed slightly from above and from the right.



A Staggered conformation



B Eclipsed conformation

As one methyl group in ethane is rotated with respect to the other through 360°, the molecule alternately assumes each of the forms

three times. In the arrangement *B* the hydrogen atoms are nearest. Specific names have been given to these two positions or **conformations.** The one in which the hydrogen atoms are nearest is said to be the **eclipsed conformation.** To this form there corresponds a maximum of energy since the repulsion between the hydrogen atoms is the greatest—they are arranged in pairs most closely to each other. The molecule tends to pass over from this energetically unfavourable state to the more stable state corresponding to the arrangement *A* In this conformation the hydrogen atoms are farthest apart and their interaction is reduced to a minimum; this is the **staggered conformation.**

The term conformation is generally used to designate any form in which the molecule can exist upon rotation of any of its part about

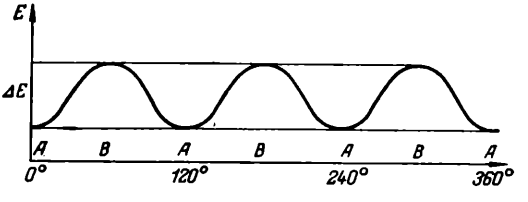


Fig. 4.2.

Potential energy barriers to interconversion of the conformations of ethane.

the single bond. Often, for the sake of brevity, only those forms are called conformations, which correspond to energy minima and are, in fact, realizable.

The rotation in ethane is thus found to be not quite free. The energy minimum (energy valley) corresponds to the staggered conformation, and the maximum energy (energy peak) to the eclipsed conformation, the energies of the other forms assuming intermediate values. The energy of the ethane molecule varies, depending on the angle of rotation of one methyl group with respect to the other, in a sinusoidal curve (Fig. 4.2). The change in energy of the ethane molecule in going from the eclipsed to the staggered conformation (ΔE) is about 3 kcal/mole and, hence, a corresponding energy must be provided from without for the molecule to pass over the energy barrier of the eclipsed conformation (the flip from the eclipsed to the staggered conformation occurs spontaneously with the liberation of energy). At room temperature and even at much lower temperatures this rotational barrier is easily overcome. In order to prevent free rotation at 20°C the height of potential energy barrier must be 25 to 30 kcal/mole, but even these barriers are not sufficient for the existence of so-called **rotational isomers** (*conformational isomers* or *conformers*) as individual chemical substances.

Let us now consider the conformations of *n*-butane caused by rotation of the ethyl groups with respect to each other about the central C—C bond. Below are shown three eclipsed (*A'*, *B'*, *C'*) and three staggered (*A*, *B*, and *C*) conformations formed from the starting conformation *A* upon rotation through 360°. The interaction between the non-bonded groups increases with increasing bulkiness. Therefore, the fully eclipsed conformation *C'* has the highest energy, the other two (*A'* and *B'*) being equivalent. The equivalent staggered conformations *A* and *C* are called **skew** (or *gauche*) **conformations** and possess a higher energy than the completely staggered or **trans conformation** *B* since an interaction between the methyl groups occurs in them, which is absent in the staggered conformation. But the difference in energy between the trans and skew conformations, ΔE, is only 0.8 kcal/mole. The energy difference $\Delta E'$ between the eclipsed conformations (for example, between *C'* and *A'*) is about 4.4-6.1 kcal/mole.

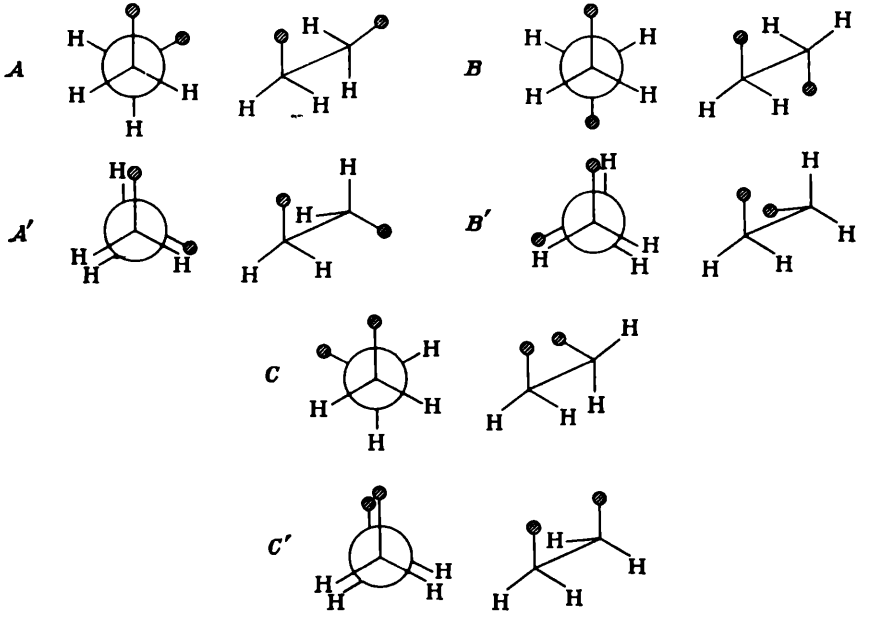


Figure 4.3 is a plot of energy change for the butane molecule upon rotation of one of the ethyl groups through 360°. The main energy peak corresponds to the completely eclipsed conformation and the main energy valley to the completely staggered conformation.

Evidently, from the qualitative aspect, the same picture must be observed for 1,2-dichloroethane and 1,2-dibromoethane; in the

case of more complex molecules a larger number of conformations must usually be taken into account.

There are two conformations (*A* and *B*) for 1,1,2-trichloroethane, both being skew conformations. In one of these conformations the chlorine atom on the rear carbon interacts with two atoms of chlorine

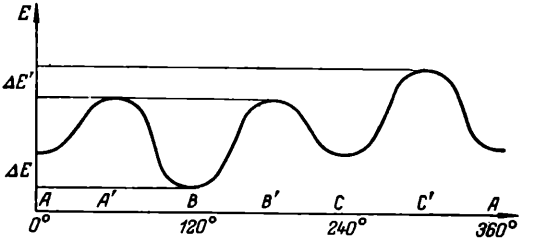
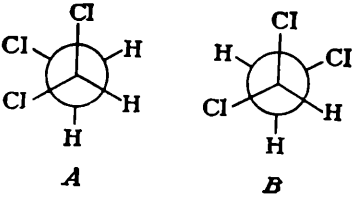


Fig. 4.3.

Potential energy barriers to interconversion of the conformations of *n*-butane.

on the front carbon; in the other, only one interaction takes place. Therefore, the conformation *B* is energetically more favourable than *A*.



The stability of conformations should be understood in the statistical sense. A molecule may adopt any conformation; but at each moment a greater part of the molecule is represented by the energetically most favourable conformation. At the next moment the percentage content of various conformations remains the same, but it does not mean that each individual molecule has not changed its conformation.

As the temperature increases the content of the less favourable conformations increases. On the contrary, with decreasing temperature the amount of the most stable conformation increases since it becomes more difficult for the molecule to overcome the potential barrier at the expense of the energy supplied by the medium. At a sufficiently low temperature the molecules assume the most favourable conformation.

It has been found that the spectra of some 1,2-disubstituted ethanes (infrared spectra, combination-scattering spectra) which have been

investigated in the liquid state contain the peaks of two conformations, while in the solid state (i.e., at lower temperatures) only the bands of one conformation are detected. In this way the bands referring to each conformation can be picked out. The relative intensity of the bands makes it possible to calculate the relative concentrations of conformations at a given temperature:

$$K = A\frac{I_g}{I_t}$$

where K = equilibrium constant (between two conformations)
I = measure of the intensity of a given line
A = a constant.

Having studied the line intensities versus temperature, we can calculate the heat of conversion, i.e., the difference between the free energies of the conformations:

$$\Delta H = R\frac{d\ln K}{d(1/T)} = R\frac{d\ln I_g/I_t}{d(1/T)}$$

Analogous conclusions can be drawn on the basis of nuclear magnetic resonance spectra (NMR spectra) if they are taken at different temperatures.

The potential energy barriers of internal rotation, which are in fact the activation energies for the conversion of one conformation into another, can also be calculated in certain cases from thermodynamic constants and from spectroscopic data on rotational energy levels. Below are given the results of calculations for some of the simplest compounds.

The energy differences between the trans and skew conformations in the gaseous state (kcal/mole) are as follows:

Butane	770 ± 90
1,2-Dichloroethane	1140 ± 20
1,2-Dibromoethane	1700 ± 40
1-Chloro-2-bromoethane	1460 ± 30
1,1,2-Trichloroethane	>2300

The potential barriers of internal rotation are (in kcal/mole):

$CH_3—CH_3$	2875 ± 126
$CH_3—CF_3$	3000 ± 200
$CH_3—SiH_3$	1300 ± 300
$CH_3—OH$	1072

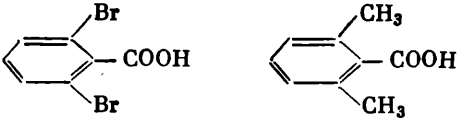
To calculate the difference in free energy between the conformations of more complex compounds and, in particular, cyclic compounds, use is made of indirect methods based on the knowledge of the energy of steric interactions between individual atoms in the simplest compounds. For the majority of cases, however, a qualitative estimation of the relative conformation energy is sufficient.

Conformational analysis is concerned with the study of the possible conformations of a compound, selection of the preferred conformation, comparison of the conformations of transition states, and with the explanation of the direction of the reaction in terms of conformational concepts or prediction of this direction. This is especially important in the case of the alicyclic series for six-membered and larger rings. We shall consider some examples of the use of conformational analysis to account for the reactivity of acyclic compounds.

(B) Steric Hindrances

We have just dealt with the conformational analysis of some of the simplest non-cyclic compounds. As we have already seen, the concepts of conformation and conformational energy are intimately bound up with the steric interaction between atoms, or, in other words, with steric hindrances in the molecule. **Steric hindrances** were originally thought to mean the overcrowding of large atoms or groups in the proximity of the reaction centre, which spatially hinder the reaction or make its occurrence impossible. Later, in connection with the development of conformational analysis and more clear-cut conceptions of reaction mechanisms, this concept was extended: we know at present that this overcrowding near the reaction centre not only impedes the reaction but sometimes facilitates its occurrence and often exerts an influence on the direction of the reaction and on the ratio of the products formed to a no lesser extent than the polar effects.

A generalized conception of steric effects was formulated and developed mainly by Ingold and his school. Steric hindrances were originally described by V. Meyer (1894), who showed that aromatic acids containing two rather bulky substituents in the ortho-position are not esterified, say, during the prolonged boiling of an alcoholic solution of the acid saturated with hydrogen chloride and the esters of this acid are not saponified. This phenomenon is not associated with the polar effects of substituents because the carboxyl group is deactivated by both electron-accepting (NO_2, Br) and electron-releasing (CH_3) groups



Meyer ascribed this phenomenon to the shielding of the reaction centre by substituents which create steric hindrances to the approach of the attacking agent. The number of such facts gradually increased.

On the other hand, the development of kinetic methods has made it possible to quantitatively compare the reactivities of compounds with different "steric strains" and modern conceptions of reaction mechanisms have made possible the relating of steric effects to transition states. Finally, the concepts of conformational analysis have been worked out. All this taken together has enabled us to approach the problem of steric effects and, in particular, steric hindrances from a more general modern viewpoint.

As has been pointed out earlier (see Volume I, page 120), every reaction is characterized by a certain definite structure and energy of the transition state. The higher the free-energy difference between the starting molecule and the transition state

$$\Delta F = F_n - F_m$$

the slower the reaction and the higher its activation energy. The height of potential energy barrier increases with increasing energy of the transition state and diminishes with increasing energy of the molecule. Therefore, any steric changes in the molecule, which bring about an increase in the transition-state energy, may be referred to as steric hindrances. Steric hindrances of this kind are termed **kinetic steric** effects since they are associated with the change of the activation energy. There also exist **thermodynamic steric** effects (including steric hindrances) which are associated, say, with the blocking of the reaction centre by bulky substituents which make difficult the approach of the reagents to the site of reaction. As we shall see below, kinetic steric effects cannot only impede but also speed up reactions.

(C) Steric Effects in Nucleophilic Substitution Reactions

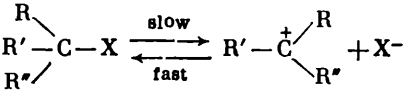
As known, a nucleophilic substitution reaction may proceed by the unimolecular (S_N1) or bimolecular (S_N2) mechanism. As an example, let us consider the most thoroughly studied case of nucleophilic substitution—the exchange of a halogen in alkyl halides for other anions. By choosing the appropriate conditions (solvent, the ratio of reagents), it is possible to bring almost any alkyl halide into reaction by the bimolecular (S_N2) mechanism. Especially liable to reactions by this mechanism are primary alkyl halides. Below are given the relative rates of three reactions proceeding (as has been established by kinetic studies) by the bimolecular mechanism for some alkyl halides:

R	$RBr+Cl^-$	$RBr+\overset{*}{B}r^-$	$RBr+\overline{O}C_2H_5$
C_2H_5	100	100	100
n-C_3H_7	65	65	28
$(CH_3)_2CHCH_2$	15	3.3	2.98
$(CH_3)_3CCH_2$	0.0026	0.0015	0.000424

As can be seen from these data, as the degree of branching of the radical increases the rate of all the three reactions falls off. This may also be attributed to the increase of the positive inductive effect in the series ethyl-neopentyl. The inductive effects of these radicals, however differ little from one another since the branching increases not at the reaction centre. The reaction rate increases especially sharply in going from isobutyl to neopentyl, in which case the inductive effect must not change noticeably, but a strong increase of the strain of the molecule and transition state should be expected. But whose energy and strain increases to a greater extent—those of the molecule or of the transition state?

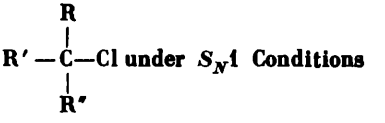
The transition state for the bimolecular mechanism has the structure shown in Volume I (page 120). Four atoms (the carbon atom, which is the reaction centre, and three carbon atoms attached to it) lie in the same plane, while the entering and leaving groups are arranged along a straight line perpendicular to this plane. It is essential that the central carbon atom is linked to five groups in the transition state and to only four groups in the original molecule. Therefore, any increase in the bulk of these groups will have a stronger effect on the strain of the transition state; the larger the bulk of the substituents the higher the potential barrier and activation energy and the slower the reaction. Thus, in the case of the S_N2 mechanism the steric strains in the proximity of the reaction centre will act as steric hindrances, which is what actually takes place.

The reverse situation occurs for the unimolecular mechanism. The first stage of the process is the ionization in the solvent:



This is the slow and rate-determining step of the reaction. In the starting compound the valence angles are tetrahedral (about 109°); in the carbonium ion, which assumes a planar configuration in the ideal case, the valence angles are 120°. Hence, the strain of the molecule caused by the mutual repulsion of the substituents, will be greater in the starting molecule than in the cation, and an increase in the size of the substituents must increase the energy of the original molecule to a greater extent. Table 4.13 gives the relative rates of hydrolysis of alkyl halides containing different radicals under the conditions of the S_N1 mechanism. Slight changes in the bulk of the radical (examples 1-4) have an insignificant effect on the reaction rate: the contributions of the steric and polar effects are commensurate. When a *tert*-butyl radical is introduced (example 5) in place of the methyl group, the reaction rate increases by a factor of more than 5. Especially great is the increase of the reaction rate in examples

TABLE 4.13. Relative Rates of Hydrolysis of Alkyl Chlorides

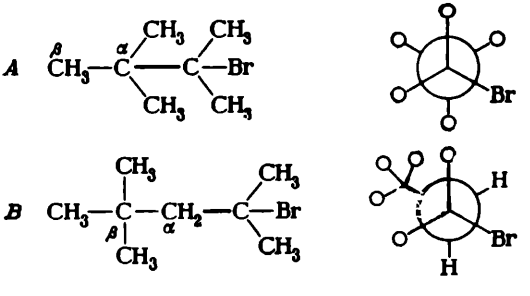


R′—C(R)(R″)—Cl under S_N1 Conditions

Example No.	R	R′	R″	Rate of hydrolysis		
				in 80% ethanol		in 90% acetone
				at 25°C	at 35°C	at 25°C
1	CH_3	CH_3	CH_3	1.00	1.00	1.00
2	CH_3	CH_3	C_2H_5	0.87-0.67	0.86	1.8-2.5
3	C_2H_5	C_2H_5	C_2H_5	3.00	2.00	—
4	C_2H_5	C_2H_5	$(CH_3)_2CH$	—	2.6	—
5	CH_3	CH_3	$(CH_3)_3C$	5.7	—	—
6	CH_3	CH_3	$(CH_3)_3CCH_2$	21	—	—
7	CH_3	$(CH_3)_2CH$	$(CH_3)_2CH$	14	—	—
8	CH_3	$(CH_3)_2CH$	$(CH_3)_3C$	—	—	1280
9	$(CH_3)_3C$	$(CH_3)_3C$	$(CH_3)_3C$	—	590	—
10	CH_3	$(CH_3)_3CCH_2$	$(CH_3)_3CCH_2$	580	—	—

8-10, which suggests that not the inductive effects but the steric effects play a part.

Still another interesting conclusion can be made on the basis of the examples given: the strain of the molecule is mainly affected by the branching at the β-carbon atom and not at the α-carbon atom (relative to the reaction centre). Thus, in example 10 the rate is approximately 45 times greater than in example 7. This fact, though strange at first sight, becomes understandable if the conformational analysis of compounds with α- and β-branching is carried out. Let us compare the formulas and conformations of two such compounds (the bond, along which the molecule is viewed, is drawn as a heavy line; the methyl groups are denoted by circles)

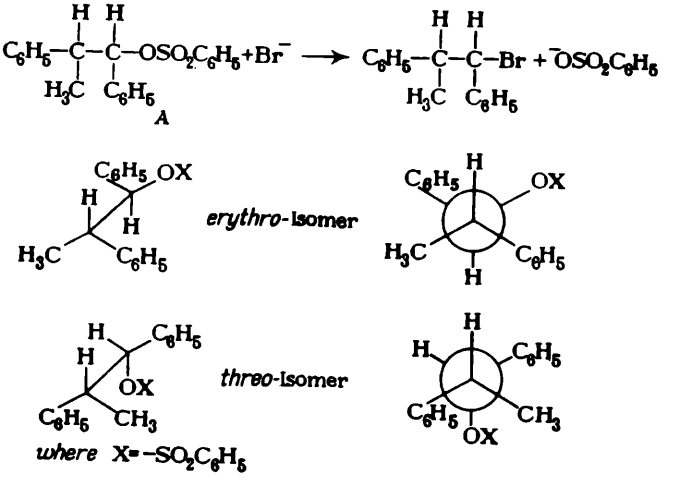


In the first case (A), when the three methyl groups are in the α-position, there are six moderate interactions in the conformation between groups of equal size (skew interactions of the butane type). In the second case (B) there are two strong interactions between the *tert*-butyl group and the methyl groups. These interactions must be stronger than all the others taken together.

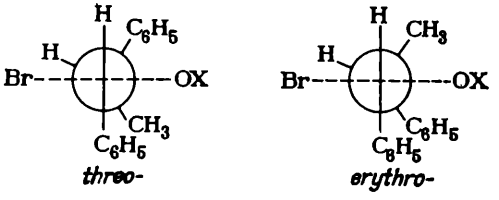
In general, we may conclude that an increase in the strain of the alkyl halide molecule caused by the mutual repulsion of atoms and groups leads to an increase in the rates of reactions proceeding by the unimolecular S_N1 mechanism. Such a phenomenon is called **steric acceleration.** The halide ion is, as it were, pushed out physically from the sterically strained molecule. It should be noted that the branching of the molecule must be sufficiently high for this effect to be evident.

Some Examples of Conformational Analysis. Consideration of the steric effects and interactions in molecules in their different conformations and in the conformations of transition states allows us to predict or account for the reactivity of various stereoisomers or the stereospecificity of the various types of reactions. Some examples of this kind are given below.

Example 1. The reaction of the *erythro*- and *threo*-isomers of compound A with lithium halides in acetone (a bimolecular reaction) has been studied and it has been shown that the *threo*-isomer is considerably more reactive than its *erythro* counterpart. This should be expected on the basis of the conformational analysis of the transition states of both isomers in this reaction (the C_6H_5 group is the most bulky substituent; the most favourable conformations are shown):



In the transition state, under the conditions of the S_N2 mechanism, the three non-changing bonds (C—phenyl, C—H and the bond with a secondary carbon atom) must lie in the same plane. The bromide ion must attack the molecule from the least sterically hindered side, i.e., must counteract the hydrogen atom (with which it will be in the eclipsed position). Below are shown the transition states for the *threo-* and *erythro*-isomers:



threo- *erythro-*

Since the phenyl is more bulky than the methyl group, it is evident that the transition state for the *threo*-isomer is more favourable (less strained) than for the *erythro*-isomer. The rate of the reaction of the *threo*-isomer is therefore greater.

Example 2. Esters of succinic acid are coupled on heating in the presence of a peroxide. The reaction evidently yields free radicals which then unite with one another:

$$\begin{array}{l} CH_3OOC-CH\cdot \\ \quad\quad | \\ CH_3OOC-CH_2 \end{array} \quad \begin{array}{l} \cdot CH-COOCH_3 \\ \quad\quad | \\ CH_2-COOCH_3 \end{array} \rightarrow \begin{array}{l} CH_3OOC-\overset{*}{C}H-\overset{*}{C}H-COOCH_3 \\ \quad\quad\quad\quad | \quad\quad | \\ CH_3OOC-CH_2 \quad CH_2-COOCH_3 \end{array}$$

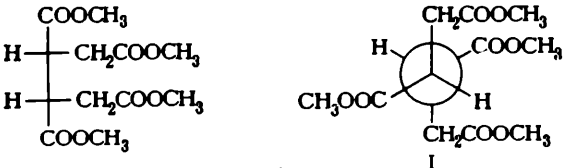
Dimer

As a result of the reaction, two asymmetric centres appear in the molecule. The stereochemical ratio in the dimer molecule is the same as in tartaric acid; to the formula of the dimer there correspond three stereoisomers: D-, L-, and the *meso* form.

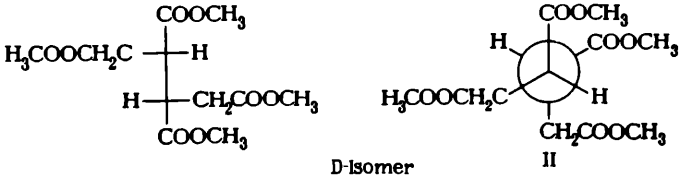
Since the asymmetric centres appear as a result of the synthesis (the starting molecules contained no asymmetric centres), the ratio of the D- and L-forms in the reaction products must be 1 : 1 (a racemic mixture). The amount of diastereomers—the *meso* form and the racemate—depends on steric factors.

Below are shown the Fischer and Newman projection formulas for the *meso* form and one of its antipodes. The Newman formulas are given for the most favourable conformations (the conformations arising from those given by rotation about the central C—C bond through 120° are unfavourable since one of the bulky groups on the front carbon atom will be arranged between the two groups of the

rear carbon atom):



meso-Form I

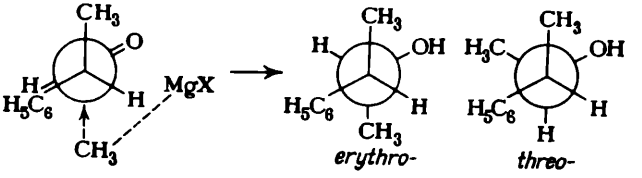


D-Isomer II

The overall rate of the reaction is determined, as is always the case, by the rate with which radicals are formed. But the relative rate of formation of the *meso* form or racemate depends on how these radicals can most favourably combine with each other, in other words, on the energy of transition states leading to conformations I and II. Which of these conformations has a lower energy? An answer to this question can be given even without knowing the relative sizes of the groups $COOCH_3$ and CH_2COOCH_3. What is important here is that one of them is more bulky than the other and, hence, a stronger interaction characterizes the conformation II, in which the identical substituents are in the skew position. One of the general rules of conformational analysis consists in that the energy of a conformation is largely determined by the strongest interaction. For instance, if the $COOCH_3$ group is more bulky than the others, conformation II is less favourable since such groups are in the skew position in it, while in conformation I they are far apart from one another. If the CH_2COOCH_3 group is more bulky, the same reasoning applies to it. Thus, conformation I must predominantly be formed, i.e., the *meso* form, which is what actually takes place: 98 per cent of the *meso* form and only 2 per cent of racemic mixture are formed.

Example 3. It is known that if, as a result of the reaction, a new asymmetric centre appears next to the existing asymmetric carbon atom, unequal amounts of two possible diastereomers are usually formed. Suppose that a Grignard reagent adds on to 2-phenylpropionaldehyde; two stereoisomeric alcohols (*erythro-* and *threo-*) may

result from this reaction:



According to Cram's rule (the rule of steric control of asymmetric synthesis), the major product of the reaction is the isomer formed by the approach of the entering group (CH_3 in this case) from the least hindered side of the double bond when the latter is flanked by the two smaller groups of the asymmetric centre. The two smaller groups in the case under consideration are H and CH_3, and the most favourable conformation is one in which oxygen is situated between these groups. In this case, the least hindered side for attack is the one between the phenyl group and the hydrogen. As a result, the *erythro*-isomer is predominantly formed, which is clear from the scheme given above.

In the consideration of steric effects we digressed from polar effects and gave examples in which they did not play an important part. It should be kept in mind that polar effects come into the scene and begin to predominate over steric effects once a strong electron-accepting substituent appears near the site of the reaction centre.

Conformational analysis is widely used to account for or predict the direction of certain rearrangements and to predict configurations formed as a result of asymmetric synthesis and occasionally even to determine the absolute configuration. This method has been worked out most extensively in application to alicyclic compounds, especially those containing six-membered rings. Steric hindrances will also be encountered when dealing with aromatic compounds in the discussion of the ortho effect and the steric hindrance of conjugation (see Volumes III and IV).

ALICYCLIC COMPOUNDS

Chapter 5

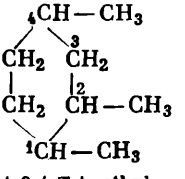
Introduction

Compounds which contain a ring built up entirely of atoms of one kind, namely, carbon atoms, are often described as **alicyclic compounds.** The prefix *ali-* is added because of their similarity to aliphatic compounds. Such compounds together with benzene and its derivatives, which constitute the large and important class of *aromatic compounds* (see Volume III), are collectively called **carbocyclic** or **homocyclic compounds.** Alicyclic compounds with properties similar to the corresponding open-chain compounds stand in contrast to the benzene derivatives with their sharply differing properties and are therefore considered separately.

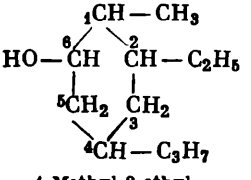
The first carbocyclic system of established structure in the history of chemistry was benzene for which Kekulé in 1865 suggested a formula of a six-membered ring (made of 6 CH groups) with three alternating double bonds. A large number of compounds containing six-membered rings were described in the succeeding years. It was thought for a certain period of time that only six-membered rings were possible and the chemists felt uncertain as regards rings with a larger or lesser number of atoms. But as the facts were accumulated these artificial barriers were overcome: three- and four-membered carbocyclic compounds became known in the period of 1882-1885 (M. Freund, W. H. Perkin, Jr.) and also derivatives of five-membered cyclopentane (W. H. Perkin, Jr.); in 1895 V. V. Markovnikov synthesized cycloheptane with a seven-membered ring, thereby breaking the ground for compounds on the other side of the six-membered ring. A large number of large rings (macrocyclic compounds) were discovered subsequently; Ruzicka synthesized all cycloalkanes containing up to 24 carbon atoms and a 34-membered ring compound; at present it is clear that there is no limit to the size of the ring.

5.1. Nomenclature of Alicyclic Compounds

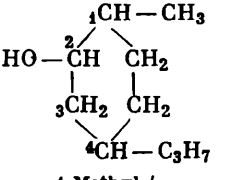
Alicyclic compounds differ by the number of members in the ring and by the number of cyclic groupings in the compound. Monocyclic compounds are named in accordance with the general rules of Geneva nomenclature, but the main chain is the chain of atoms contained in the ring; their names are formed by attaching the prefix *cyclo* to the names of the acyclic saturated hydrocarbons (alkanes) with the same number of carbon atoms as there are in the ring. Their derivatives are named in the same way as their acyclic analogues. Substituents are assigned numbers consistent with their positions in such a way as to keep the sum of the numbers to a minimum. For example,



1,2,4-Trimethylcyclohexane

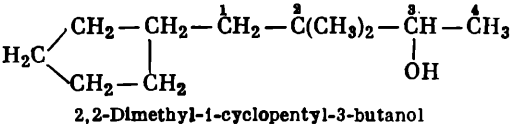


1-Methyl-2-ethyl-4-propyl-6-cyclohexanol



1-Methyl-4-propyl-2-cyclohexanol

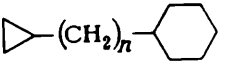
But when the side chain is too long and complex, this method of numbering is inconvenient; in such cases the open chain is named according to the rules of Geneva nomenclature, and the ring is regarded as a substituent in the principal chain. For example,



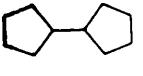
2,2-Dimethyl-1-cyclopentyl-3-butanol

Polycyclic compounds may be divided into the following principal groups:

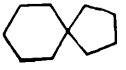
(a) compounds with isolated rings separated by a chain of carbon atoms:



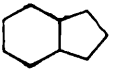
(b) compounds with rings connected by a single carbon-carbon bond:



(c) compounds with rings having one common atom (**spirans**):

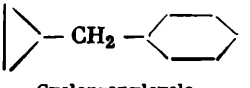


(d) compounds with rings having two common atoms:

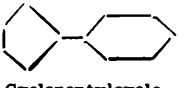


(e) compounds with more than two common atoms in the ring (**bridged compounds**):

For the first two groups use is made of the rational or systematic nomenclature; for example,

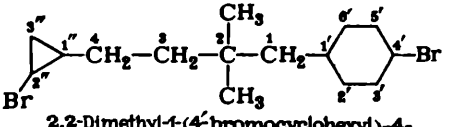


Cyclopropylcyclohexylmethane



Cyclopentylcyclohexane

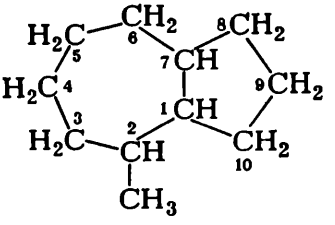
In more complicated cases, the main chain connecting the rings is numbered as usual and the carbon atoms in each ring are given primed numbers:



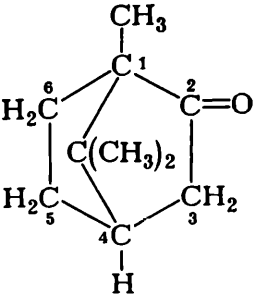
2,2-Dimethyl-1-(4′-bromocyclohexyl)-4-(2″-bromocyclopropyl)-butane

The nomenclature of the last two groups (*d* and *e*) is as follows. All such compounds are regarded as bridged compounds, the numbering is started from one of the key atoms, continued along the longest bridge and then returned to the starting atom by the longest path; then the atoms of the smaller bridge are numbered. If there are branchings in the ring, the numbering is started from the key carbon atom which is nearest to the branching. The name of the main chain is preceded by the prefix *bicyclo* followed by a numeral in square brackets indicating the number of atoms in each bridge. The key atoms, i.e., atoms standing at the head of the bridge, are not included

with the bridge atoms:



2-Methylbicyclo [5.3.0]decane



1,7,7- Trimethylbicyclo [2.2.1]-heptan-2-one (camphor)

In the alicyclic series, use is often made of trivial names and of the numbering of atoms conventional for a given parent hydrocarbon; this is particularly used for terpenes and other natural compounds (see Volume IV).

5.2. Structure of Alicyclic Compounds

It was originally thought (Baeyer) that all the atoms in the ring lie in the same plane. From this it follows that the bond angles are: 60° in the three-membered ring; 90° in the four-membered ring; 108° in the five-membered ring; 120° in the six-membered ring, etc. But the chains of saturated carbon atoms are characterized by the tetrahedral angle of 109°28′ (which is recognized as the normal angle between the four bonds to a saturated carbon atom), and in 1885 Baeyer suggested that the greater the deviation of the bond angle in the ring from the tetrahedral angle the greater is the strain and the lower is the stability of the ring. He proposed that one half of the difference between the tetrahedral angle and the bond angle — the quantity α which expresses the deviation of one valency from the normal value—be regarded as a measure of the strain set up in the molecule:

n	3	4	5	6	7	8	9
α	24°44′	9°44′	0°44′	−5°16′	−9°33′	−12°46′	−35°16′

The C—C—C angle in cyclopentane differs least from the tetrahedral angle, and the three-membered ring and large rings (if they are planar) are under the greatest strain.

From the values of Baeyer strain it follows that cyclopentane must possess the lowest energy and cyclopropane and large rings the highest energy. This was more or less in qualitative agreement with the data available at that time since large rings were not known. Indeed,

the cyclopropane ring is capable of being opened by the action of hydrogen halides and bromine and is readily hydrated catalytically; cyclobutane is considerably more stable; cyclopentane is exceedingly stable as should be expected, the stability of its ring being reminiscent of the stability of the ordinary paraffin chain. Cyclohexane was thought to be the only exception: its ring is no less stable than the cyclopentane ring and is formed in cyclization reactions more readily than the others. Synthesis of medium-sized rings (8- to 14-membered) was found to be a rather formidable task; only cycloheptane was obtained relatively early by Markovnikov (1893). The difficulty of their preparation seemed to support the Baeyer strain theory.

In 1890 Sachse postulated that cyclohexane could have a nonplanar arrangement of ring atoms. But the majority of scientists continued to support the earlier views until in 1918 Mohr revived and supported with further evidence Sachse's suggestion as to the spatial arrangement of atoms in cyclohexane and proposed two possible models (two so-called *puckered* or *folded* forms) for its ring structure: the **boat** and **chair forms** which are both free from the Baeyer angle strain.

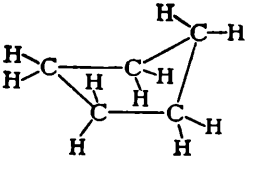
A sufficiently large amount of data had accumulated by that time, which contradicted the Baeyer strain theory. As has already been pointed out, cyclohexane is not inferior in strength and ease of formation to cyclopentane. Furthermore, judging by the heats of combustion calculated per methylene group, the energy values for the cyclopentane ring and larger rings are very close to one another (see Table 6.2), whereas according to Baeyer's strain theory the reactivity or energy content must gradually increase with increasing ring size. Finally, some larger rings were obtained, whose stability did not differ from the stability of cyclohexane or of aliphatic isologues. The structure of cyclohexane was later confirmed by spectroscopic data. It became clear that its sufficiently large ring is twisted in space, tending to assume such a form in which the angles are equal or close to the tetrahedral angle. The relative difficulty of preparation of large rings was attributed to the low probability of encounter of the terminal groups of the molecule being cyclized (this probability decreases with increasing chain length).

XX. Conformational Analysis of the Simplest Alicyclic Compounds

Apart from the angle strain, in cyclic compounds there also exists a strain associated with the fact that hydrogen atoms are partly or completely in the eclipsed position: in cyclopropane, cyclobutane,

and cyclopentane each hydrogen atom is practically in contact with the two neighbouring atoms. For cyclopropane, to the angle strain energy is added the energy of mutual repulsion of three pairs of hydrogen atoms. In cyclopropane, each carbon atom is linked to the other two and there is no non-bonded interaction between the carbon atoms. The situation is different with cyclobutane, in which apart from the angle strain and the energy of interaction of four pairs of hydrogen atoms (strain due to eclipsing of adjacent hydrogen atoms), there is a certain additional strain due to the interaction between the first and fourth carbon atoms which are only 2.2 Å apart from each other (bond opposition strain). Theoretical calculation of the sum of all the strains in cyclobutane yields a value which by far exceeds the experimental value obtained from thermochemical data. Therefore, at present it is generally agreed that one of the ring atoms in cyclobutane is slightly out of the plane of the other three atoms. This out-of-plane position reduces the total strain energy of cyclobutane. The strain of the molecule, which twists one of the atoms out of the plane of the ring, is known as **torsional strain** (or *Pitzer strain*).

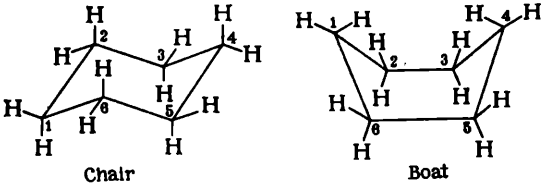
In cyclopentane, there is almost no angle strain (0°44′), but the torsional strain is considerable. It is associated with the mutual repulsion of five pairs of hydrogen atoms which are in the eclipsed position. As a result, one of the ring atoms comes out of the plane of the ring by 0.5 Å, though such a distortion of the ring increases somewhat the angle strain. The nonplanar arrangement of atoms in cyclopentane has been proved by the electron diffraction method. The cyclopentane molecule is flexible so that any one carbon atom may assume the out-of-plane position: the ring is in a constant wave-like motion.



In a first approximation, which is quite suitable for chemical purposes, the skeletons of cyclobutane and cyclopentane may be represented as lying in a single plane.

To avoid angle strain, the cyclohexane ring can assume two conformations—the **boat** and **chair** forms (Mohr, 1919). In one of them (the boat form) four carbon atoms lie in the same plane, and two atoms are in the out-of-plane position; in the chair form there are two parallel planes each containing three carbon atoms.

The chair and boat forms are both completely free of angle strain, but they differ in energy content. The study of cyclohexane with



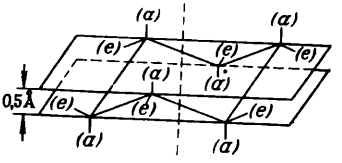
the aid of combination scattering spectra (Kohlrausch, 1963) and later by means of infrared spectra and electron diffraction has shown that, within the accuracy limits of these methods, the cyclohexane molecules are mainly in the chair conformation. This means that the chair conformation is energetically more favourable (more stable) than the boat form (the flexible form).

Let us consider successively every two carbon atoms of cyclohexane with their bonds as the secondary carbon atoms of the butane molecule (see page 192). Then, in the case of the chair form we shall invariably mean the skew (or gauche) conformation of the butane type. In the chair conformation, the cyclohexane molecule will have six relatively weak skew interactions. Indeed, as follows from the three-dimensional spatial model, the bond directions in the chair form alternate in space. In the boat conformation there are four skew interactions and two eclipsed butane-like interactions; these eclipsed interactions sharply increase the energy of this conformation. Indeed, such interactions are revealed if the bonds 2-3 and 5-6 are considered in the same way as the bonds between the secondary carbon atoms in butane. The interaction energy for methyl groups in the skew butane-like conformation is assumed to be equal to 0.8 kcal/mole and that in the eclipsed conformation, to 4.4-6.1 kcal/mole. Hence, the difference in energy content between these conformations ranges from 7.2 to 10.6 kcal/mole:

$$2 \times 6.1 + 4 \times 0.8 - 6 \times 0.8 = 10.6 \text{ kcal/mole}$$

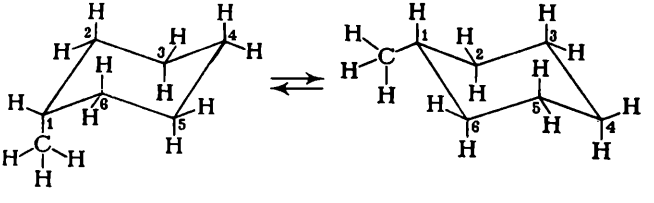
This method of calculation is arbitrary since the skew interaction in butane is caused by the presence of three hydrogen atoms in the methyl group, and in cyclohexane only methylene groups (each containing two hydrogen atoms) interact with one another; but the method is justifiable in comparing the energy content of the chair form with that of the boat form since these differences cancel in subtraction.

Thus, in the more favourable chair conformation the carbon atoms are arranged in two parallel planes (three atoms lying in each plane), the threefold axis of symmetry passing perpendicular to them. The distance between the planes is about 0.5 A.



The twelve C—H bonds of cyclohexane are not equivalent; there are two sets of six bonds. In one of these sets the six bonds are parallel to the axis of symmetry (and to one another) and are called **axial bonds** (labelled *a*). In the other set the six hydrogen atoms are linked by **equatorial bonds** (*e*) directed at an angle of 109.5° to the axis of symmetry.

The cyclohexane molecule can assume two completely equivalent chair conformations. Upon conversion of one chair conformation into the other chair form the axial hydrogen atoms become equatorial and vice versa. In a substituted cyclohexane (for example, in methylcyclohexane) the two forms are no longer equivalent since in one of them the methyl occupies the axial and in the other the equatorial position:



If the methyl is axial, two extra skew butane-like interactions occur between the methyl and methylene groups in positions 3 and 5. There are no such interactions in the equatorial conformation. Therefore, the energy difference between the conformations is approximately the doubled value of the skew butane-type interaction, i.e., $2 \times 0.8 = 1.6$ kcal/mole. Thus, the conformation of monosubstituted cyclohexanes with substituents in the equatorial position is more stable than the one in which the substituents are in the axial position.

All that has been said can be summarized as follows. Cyclohexane (and its derivatives) can assume two types of conformation: the chair and boat forms. The first is more stable (it has a lower energy) and is generally regarded as the only form in which cyclohexane actually exists. Monosubstituted chair cyclohexanes may have two conformations: one with an axial and the other with an equatorial substituent; the latter has a lower energy content.

Valuable information on the conformational equilibrium can be obtained by spectroscopic methods, in particular by the nuclear magnetic resonance method (for the NMR method, see page 292 et

seq.). As an example, we shall consider the data obtained for 1,1-difluorocyclohexane.

Figure 5.1 shows the NMR spectrum of 1,1-difluorocyclohexane (for fluorine nuclei) at different temperatures. At +30°C a single peak appears, which means that both fluorine atoms—the axial and the equatorial atom—are practically equivalent because of the rapid interconversion of the two conformations (so that one fluorine atom becomes alternately axial and equatorial). At low temperatures

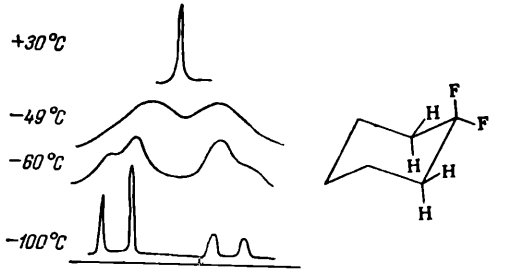


Fig. 5.1.
NMR spectra of 1,1-difluorocyclohexane.

the energy barrier between the conformations is more difficult to surmount and the lifetime of each conformation is longer. As the temperature decreases the signal widens and splits into two maxima (peaks) and, finally, at —100°C there appear two signals corresponding to two different dispositions of the fluorine nuclei (the peaks of the axial fluorine atom are somewhat widened on the right due to the spin-spin interaction with the ring protons). From the spectral data we can calculate the lifetime τ of an individual conformer at each temperature by the formula:

$$\frac{\delta_\tau}{\delta_\infty} = \left[1 - \frac{1}{2\pi^2\tau^2(\delta_\infty)^2}\right]^{1/2}$$

where δ_τ is the chemical shift between the signals of fluorine atoms at a given temperature, and δ_∞ is the chemical shift at —100°C (or at a lower temperature) when the peaks are distinctly separated.

Thus, the lifetime of a conformation at different temperatures is as follows:

°C	τ, sec	°C	τ, sec
+30	1.0×10^{-6}	—60	1.2×10^{-3}
—49	6.5×10^{-4}	—100	2.0×10^{-2}

XXI. Isomerism of Alicyclic Compounds

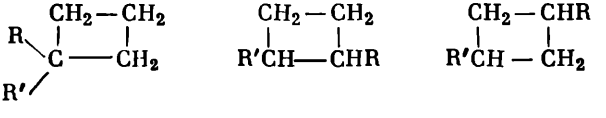
In order to understand the conformational relations in disubstituted cyclohexanes the isomerism of alicyclic compounds should first be discussed.

The following types of isomerism are known for alicyclic compounds:

1. *Ring-size isomerism* (*caused by different ring sizes*); for example, cyclopentane, methylcyclobutane, dimethylcyclopropane are all isomers with the empirical formula C_5H_{10}

2. *Side-chain isomerism* (*caused by different side-chain structures*); for example, isopropylcyclobutane, propylcyclobutane, ethylmethylcyclobutane.

3. *Position isomerism caused by the different relative arrangement of substituents in the ring.* Two isomers of this kind are possible for a disubstituted cyclopropane: 1,1- (or *gem*-) and 1,2- (or *vicinal*-). In a disubstituted cyclobutane the positions 2 and 4 are equivalent; disubstituted cyclobutanes are represented by three isomers: 1,1-, 1,2- and 1,3-:

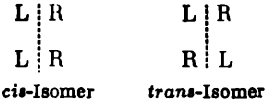


4. *Stereoisomerism.* In contrast to saturated aliphatic compounds, alicyclic compounds are characterized by geometrical *cis-trans* isomerism (if two or more substituents are present). Besides, as will be clear from the following discussion, geometrical isomerism in this case is inseparably associated with optical isomerism. The point is that, in spite of conformational rotations, which become less and less hindered as the ring size increases, all small and medium-sized rings (up to 8- or 9-membered) are, to a certain extent, rigid structures. Therefore, two substituents on two different carbon atoms of the ring can be placed on one side of the ring plane—in the *cis* arrangement (*cis*-isomer); if the substituent groups are on opposite sides, the compound is the *trans*-isomer. Of course, beginning with the six-membered ring upwards, the expression "ring plane" is conditional and one has to resort to a certain average plane of the molecule.

For the *cis*- and *trans*-isomers to be differentiated in the case of small rings (three- to five-membered rings) use may be made of the same methods as were utilized for the *cis*- and *trans*-isomers

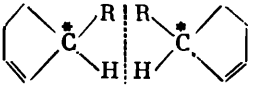
of olefinic compounds: cyclization of *cis*-substituents (for example, anhydride formation for carboxyl groups; the formation of a cyclic ester with boric acid for hydroxyl groups) and estimation on the basis of the dipole moment of the molecule. One additional method can also be used.

Monosubstituted cycloalkanes always have an axis of symmetry, which passes through the substituent, hydrogen and carbon atom, to which the first two are attached. Hence, the molecule is symmetrical and has no stereoisomers. The situation is different if a cycloalkane has two substituents, even identical but on different carbon atoms of the ring. In this case, the *cis*-compound always possesses a plane of symmetry and is thus optically inactive, and its mirror image is identical with the original molecule. The *trans*-compound, on the contrary, usually possesses no plane of symmetry; it has two asymmetric carbon atoms and its mirror image is enantiomeric (see p. 33) to the original molecule. From the standpoint of optical isomerism, a full analogy is observed in this case with tartaric acids: the *cis*-isomer corresponds to the inactive acid due to the internal compensation of mesotartaric acid, and the *trans*-isomer corresponds to the levo- and dextrorotatory tartaric acids*. If the substituents are different, both the *cis*- and *trans*-isomers always have mirror images enantiomeric to the original molecule and therefore exist in the form of four stereoisomers—two antipodes and two diastereomers, which can be pictured schematically as follows (see p. 47):



cis-Isomer *trans*-Isomer

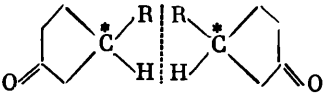
In the case of a cycloalkene with one substituent



there appears one asymmetric carbon atom and, hence, there are

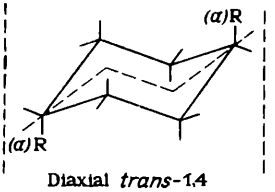
* The only exception is those disubstituted cycloalkanes with an even number of units in the ring (e.g., cyclobutanes, cyclohexanes, etc.) in which the substituents (identical or different, in the *cis*- or *trans*-position) are on carbon atoms farthest from one another. In this case, the *trans* compound too has a plane of symmetry passing through these two carbon atoms and two substituents, and this is why both the *cis* and *trans* compounds are optically inactive and have no enantiomeric forms.

two enantiomers, the levo and the dextro. In this and similar compounds, say, in substituted cycloalkanones

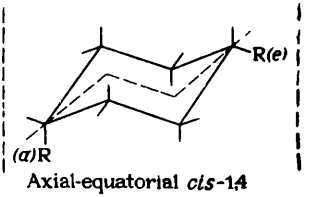


we deal with the usual optical isomerism with one asymmetric carbon atom, and this phenomenon is not associated with geometrical isomerism.

Disubstituted cyclohexanes are also characterized by geometrical and optical stereoisomerism. Since the cyclohexane ring is nonplanar, the assignment of isomers to *cis*- or *trans*-configurations is not too evident. As has already been mentioned, in the chair conformation there are two parallel planes, each of which contains three ring carbon atoms. The plane of the molecule may be considered to be the one intermediate between them. Every two neighbouring axial bonds are found to be in the *trans*-position since they are on opposite sides of this plane; this also applies to equatorial bonds, though their angles relative to the plane of the ring are considerably smaller. Therefore, 1,2-, 1,3- and 1,4-disubstituted cyclohexanes exhibit geometrical isomerism and are capable of existence in the form of the *cis*- and *trans*-isomers; 1,2- and 1,3-disubstituted cyclohexanes are characterized also by optical stereoisomerism, whereas the 1,4-isomer is devoid of such a possibility because both the *cis*- and *trans*-isomers in this case possess a plane of symmetry passing through the ring atoms 1 and 4:



Diaxial *trans*-1,4

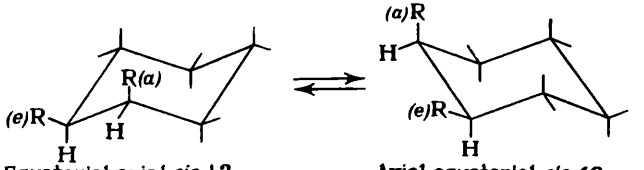


Axial-equatorial *cis*-1,4

Let us now carry out the conformational analysis of dimethylcyclohexane. The bonds that lie on one side of the cyclohexane ring (in the chair conformation) alternate at neighbouring atoms: equatorial (*e*)—axial (*a*), —*e*—*a*— and so on. Hence, in *cis*-1,2-dimethylcyclohexane one methyl is always axial and the other equatorial. When this conformation is converted into another possible chair confor-

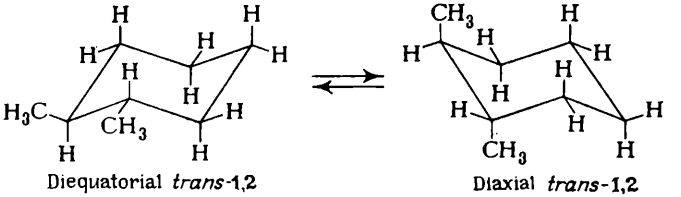
mation, the axial bond becomes equatorial and vice versa. The same situation is observed for *trans*-1,3- and *cis*-1,4-disubstituted cyclohexanes.

Hence, in these cases (*cis*-1,2-, *trans*-1,3- and *cis*-1,4-disubstituted methylcyclohexanes) there is only one conformation with one axial and one equatorial position of methyl groups; for example:



Equatorial-axial *cis*-1,2 Axial-equatorial *cis*-1,2

In the case of *trans*-1,2-dimethylcyclohexane two methyl groups are both either in the equatorial or in the axial position. Thus, we are dealing here with two nonequivalent conformations. An analogous situation is observed in *cis*-1,3- and *trans*-1,3-disubstituted cyclohexanes.


H
H
H

and 5 with respect to it). For the *cis*-1,3 and *trans*-1,4-isomers the diequatorial conformation is also found to be more favourable than the diaxial conformation.

On the basis of these considerations it is possible to predict the relative energy content of *cis*- and *trans*-isomers and, hence, their stability. For example, by comparing the most favourable conformations of 1,2-dimethylcyclohexanes (only an axial-equatorial conformation is possible for the *cis*-isomer and a diequatorial conformation for the *trans*-isomer) we come to the conclusion that the *trans*-1,2 isomer is at the lowest energy level since the axial position of the methyl group is less favourable and therefore it is more stable. In the case of 1,3-dimethylcyclohexane, on the contrary, the *cis*-isomer is at a lower energy level since it can exist in the diequatorial conformation.

It should be taken into account, however, that if the molecule has polar substituents capable of electrostatic interaction, these conclusions may prove incorrect.

Chapter 6

Alicyclic Hydrocarbons and Their Derivatives

Alicyclic hydrocarbons are light liquids (cyclopropane and cyclobutane are gases), which are immiscible with water and miscible in all proportions with the majority of nonpolar solvents. Some of the physical properties of the lower and medium-sized alicyclic hydrocarbons are listed in Table 6.1.

As has already been pointed out, the thermodynamic stability of rings is different. This can be judged by the heats of combustion (ΔH) calculated per methylene group (Table 6.2). The greatest heats correspond to cyclopropane and to cyclobutane, in which the bond angle distortion (angle strain) and the torsional strain are great. Large rings have rather close values of ΔH. There are, however, quite characteristic distinctions in this case too. Among the first ten members cyclohexane has the least energy content. The higher energy content of cyclopentane is accounted for by the torsional strain which arises, as previously discussed, as a result of the steric interaction of hydrogen atoms which are in the unfavourable eclipsed positions. In medium rings (8- to 13-membered) the heat of combustion per methylene group is slightly higher than in cyclohexane due to another type of strain, non-Baeyer strain (the interaction of hydrogen atoms situated on opposite sides of the ring); this effect will be discussed in a section devoted to large and medium-sized rings. Finally, the energy of large or macro rings is the lowest and is close to the energy content of acyclic paraffins with a normal chain.

The chemical properties of cyclopentane and higher cycloalkanes are in general similar to those of ordinary paraffins: they are difficultly oxidizable and unreactive compounds. They are chlorinated by a free-radical mechanism, can be nitrated under the conditions of the Konovalov reaction, etc. (see Volume I, page 93). The reaction of cyclopentane which indicates the presence in it of a small conformational strain is the reaction discovered by B. A. Kazansky and A. F. Plate, which is the catalytic hydrogenolysis over platinum at

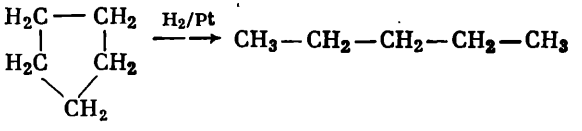
TABLE 6.1. **Alicyclic Hydrocarbons**

Formula	Name	m. p., °C	b. p., °C	Density d_4^{20}
	Cyclopropane or trimethylene	−126.6	−34.4	0.720 (at −79°C)
	Cyclobutane	−50	+13.0	0.703 (d_4^0)
	Cyclopentane	−93.3	49.5	0.7510
	Cyclohexane	6.5	81.4	0.7791
	Cycloheptane	−12	118.1	0.8099
	Cyclooctane	14.3	148 (at 749 mm Hg)	0.8350
	Cyclopropene	—	−36 (at 744 mm Hg)	—
	Cyclobutene	—	2.4	0.733 (d_4^0)
	Cyclopentene	−93.3	44.2	0.7720
	Cyclopentadiene	−85	42.5	0.8021
	Cyclohexene	−103.7	83	0.8102
	1,3-Cyclohexadiene	−89	80.5	0.8404
	1,4-Cyclohexadiene	−49.2	86-87	0.8471
	Cycloheptene	−56	115	0.8228
	1,3-Cycloheptadiene	—	121 (at 724 mm Hg)	0.8929 (d_0^0)
	1,3,5-Cycloheptatriene or tropilidene	−79.5	117	0.8875
	Cyclooctene (*trans*-)	−59	145	0.8483
	1,5-Cyclooctadiene	−57; −70	144	0.887 (d_4^0)
	1,3,5-Cyclooctatriene	—	148	0.912 (d_4^0)
	Cyclooctatetraene	−7	143	0.9206

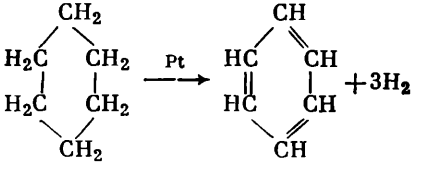
TABLE 6.2. **Heats of Combustion for Cycloalkanes per Methylene Group (kcal)**

Compound	Number of carbon atoms	ΔH	Excess energy as compared with cyclohexane (per CH_2)
Cyclopropane	3	166.6	9.2
Cyclobutane	4	163.9	6.5
Cyclopentane	5	158.7	1.3
Cyclohexane	6	157.4	0
Cycloheptane	7	158.3	0.9
Cyclooctane	8	158.6	1.2
Cyclononane	9	158.7	1.3
Cyclodecane	10	158.5	1.1
Cyclopentadecane	15	157.1	−0.3
Cycloheptadecane	17	157.0	−0.4

300°C leading to pentane:



Cyclohexane hydrocarbons (if they have no 1,1-substituents) when passed over platinum at elevated temperatures evolve 3 moles of hydrogen and are converted into hydrocarbons of the benzene series (N. D. Zelinsky):

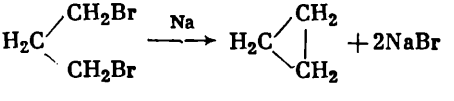


6.1. Small Rings

A. The Cyclopropane and Cyclobutane Series

(a) *Methods of Synthesis*

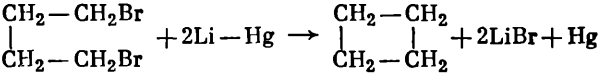
1. The action of metallic sodium on 1,3-dihalogen derivatives of alkanes leads to the formation of hydrocarbons of the cyclopropane group (Freund):



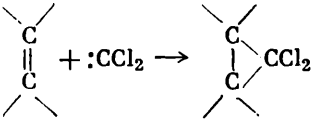
This is essentially the Wurtz intramolecular reaction.

As has been established by G. G. Gustavson, the dehalogenation proceeds with a better yield when zinc dust in alcoholic solution is used.

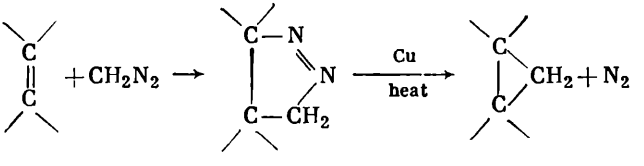
In 1967, Connor and Wilson found that 1,4-dibromobutane when reacted with lithium amalgam in dioxan or tetrahydrofuran forms cyclobutane in good yield:



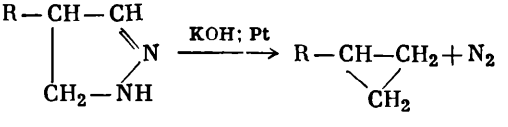
2. An important method of preparation of three-membered rings is the addition of carbenes (see Volume I, page 298; for more detail. see Volume IV) to unsaturated compounds:



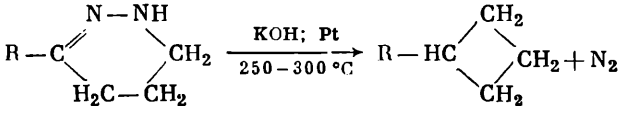
If diazo compounds are used for this purpose, then heterocyclic compounds are first formed, which on heating in the presence of copper liberate nitrogen and form derivatives of cyclopropane (Buchner and Curtius):



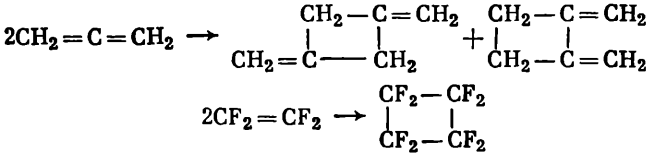
3. Three-membered rings are also obtained by the Kishner reaction through the catalytic decomposition of cyclic hydrazones:



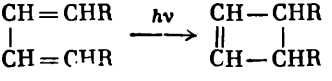
An analogous reaction has been worked out for synthesis of derivatives of cyclobutane (R. Ya. Levina and Yu. S. Shabarov):



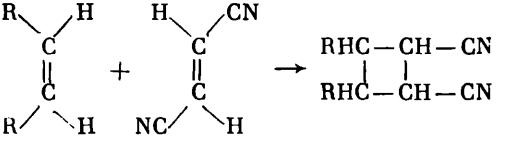
4. Dimerization of allenes (S. V. Lebedev) and also of perfluoroolefins leads to four-membered rings:



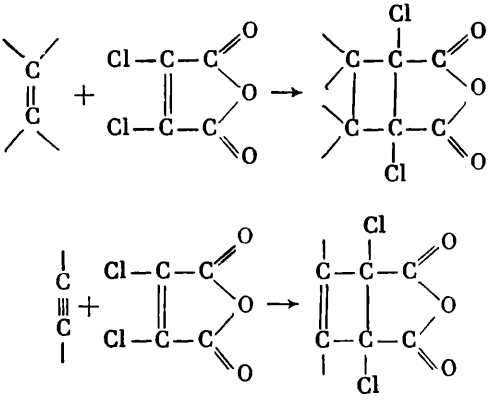
5. 1,3-Diene systems undergo cyclization to form cyclobutenes when irradiated by ultraviolet light (Dauben and Fonken):



6. Maleic anhydride and some other dienophiles when acted on by light are capable of adding on to olefins with the formation of four-membered rings; for example:

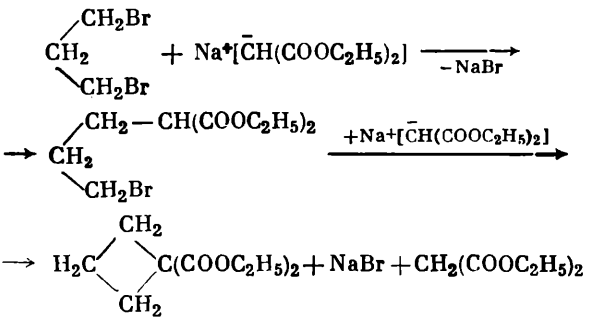


Dihalomaleic anhydride adds on to olefins and acetylenes photochemically according to the following schemes (Scharf and Cortez):



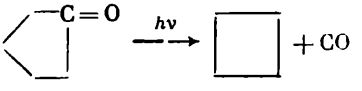
7. The oldest method of synthesis of four-membered rings consists of the interaction of sodiomalonic ester with dihalogen derivatives

of hydrocarbons (Perkin):



Sodiomalonic ester plays here the role of a base which splits off hydrogen bromide from the product of initial condensation.

8. The photolysis of cyclopentanone gives cyclobutane and carbon monoxide in addition to other decomposition products (Benson, Kistyakovsky):



(b) *Properties of Small Rings*

The strain of the cyclopropane molecule is largely accounted for by the distorted angles between the C—C bonds—by the mutual repulsion of the electron orbitals of these bonds. As a result, the

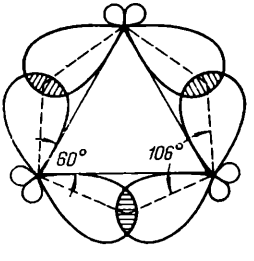
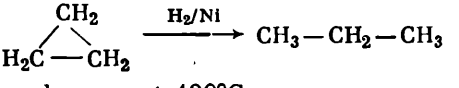


Fig. 6.1.
Bent or "banana" bonds in cyclopropane.

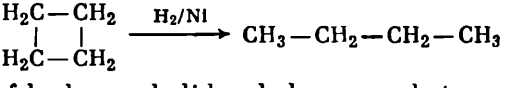
bonds (i.e., the maxima of overlap of electron orbitals) are not on straight lines connecting the centres of carbon atoms but arrange themselves at a certain distance—beyond the triangle of the molecule (Fig. 6.1). In spite of the fact that with such a distortion of the electron orbital the overlap becomes less complete, this disposition of

bonds proves to be more favourable energetically. Thus, according to the modern conceptions, the σ-bonds in cyclopropane differ from ordinary σ-bonds* and their hybridization is different from ordinary sp^3 hybridization. These bonds are known as *bent* or **banana bonds** (the banana-like electron orbital of the distorted σ-bond) and, in fact, occupy an intermediate position between the ordinary σ- and π-bonds. This is reflected in the many properties of cyclopropane, especially in its ability to conjugate with multiple bonds (see below). The angle between the bonds in cyclopropane is 106° instead of 60° according to classical conceptions, and the H—C—H bond angle is about 120°. Owing to this structure cyclopropane is capable of entering into electrophilic addition reactions and resembles compounds with double bonds in this respect (though they are much less active than the latter).

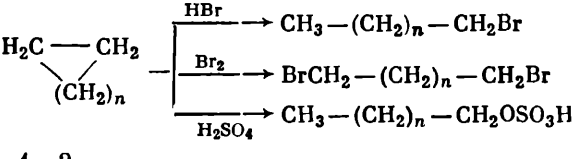
Cyclopropane is hydrogenated over nickel with rupture of the C—C bond at 80° C:



while cyclobutane does so at 120°C:

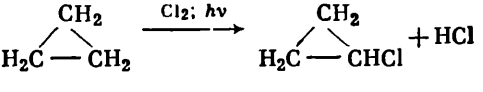


The action of hydrogen halides, halogens and strong mineral acids can bring about a rupture of three- and four-membered rings (in this reaction cyclobutane reacts more sluggishly than cyclopropane):

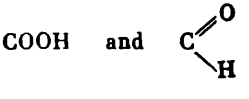


where $n = 1, 2$.

In the reaction with chlorine, apart from the ring disclosure, there takes place the replacement of hydrogens (metalepsy):

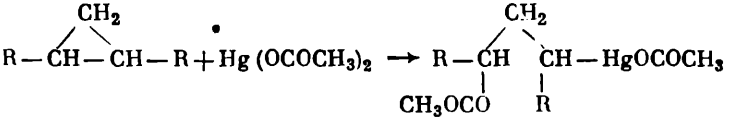


It is interesting that the presence of electron-withdrawing substituents such as, for example,

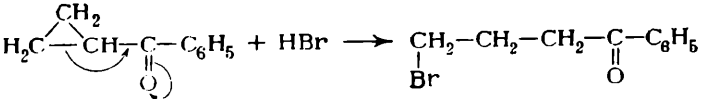


* In cyclobutane, the sigma-bonds are also bent relative to the C—C axis, but this bond distortion is insignificant.

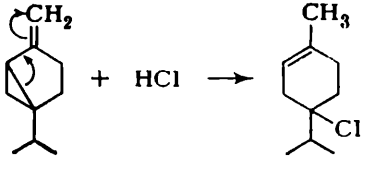
makes the disclosure of rings very difficult. On the contrary, the presence of alkyl substituents facilitates these reactions. For instance, alkylsubstituted cyclopropanes readily add mercuric acetate (R. Ya. Levina):



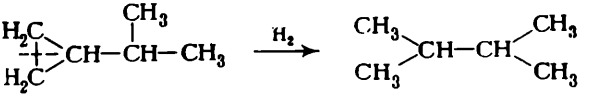
Thus, many reactions of the cyclopropane ring point to its analogy with the double bond. Especially characteristic is the conjugation with multiple bonds. For example, the addition of hydrogen bromide to benzoylcyclopropane proceeds contrary to Markovnikov's rule:

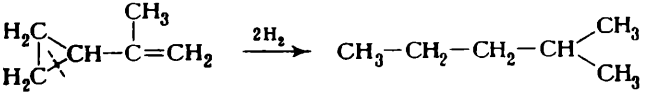


Hydrogen chloride adds on to sabinene at the extreme atoms of the conjugated cyclopropane-double bond system:



The hydrogenation of isopropylcyclopropane and isopropenylcyclopropane leads to the various products due to the presence of conjugation in the second compound (B. A. Kazansky and M. Yu. Lukina):





The conjugation of cyclopropane with a double bond can be recognized by the shift of the absorption peaks in the infrared and ultraviolet spectra. Thus, even from spectroscopic data one can judge whether the double bond is conjugated with or isolated from the ring.

Cyclopropane is a gas (b.p. —35°C); it is used extensively as a general anaesthetic in surgical operations; its advantage is that it is completely non-toxic to the body and does not cause undesirable aftereffects. Cyclopropane is produced on an industrial scale by the Gustavson method: by the action of zinc on 1,3-chlorobromopropane, which is synthesized by adding hydrogen bromide to allyl chloride in the presence of a source of free radicals—benzoyl peroxide:

$$ClCH_2-CH=CH_2+HBr \longrightarrow ClCH_2-CH_2-CH_2Br$$

$$ClCH_2-CH_2-CH_2Br \xrightarrow{Zn} H_2C\begin{array}{c}CH_2\\/\quad\backslash\\-\quad-\end{array}CH_2$$

B. Unsaturated Three- and Four-Membered Rings

Cyclopropene and **cyclobutene** have been prepared by the decomposition of cycloalkyltrimethylammonium hydroxide on heating:

$$H_2C\begin{array}{c}CH_2\\/\quad\backslash\\-\quad-\end{array}CH-\overset{+}{N}(CH_3)_3OH^- \xrightarrow{t^\circ} HC\begin{array}{c}CH_2\\/\quad\backslash\\=\quad-\end{array}CH + N(CH_3)_3 + H_2O \quad \text{(Demyanov)}$$

$$H_2C\begin{array}{c}CH_2\\|\quad|\\-\quad-\end{array}CH-\overset{+}{N}(CH_3)_3OH^- \xrightarrow{t^\circ} HC\begin{array}{c}CH_2\\|\quad|\\=\quad-\end{array}CH \quad \text{(Roberts)}$$

These compounds are unstable, particularly cyclopropene, which is readily polymerized.

More stable derivatives of cyclopropene are known. They can be prepared, for example, by the reaction of certain carbenes with derivatives of acetylene:

$$C_6H_5-C\equiv C-C_6H_5 + \overset{\cdot\cdot}{C}Cl_2 \xrightarrow[(from\ CHCl_3)]{} C_6H_5-C=\underset{\backslash\quad/}{C}-C_6H_5 \xrightarrow{H_2O} C_6H_5-C=\underset{\backslash\quad/}{C}-C_6H_5$$

$$Cl\quad Cl \qquad\qquad O$$

$$C_6H_5-C\equiv C-C_6H_5 + \overset{\cdot\cdot}{C}HCOOC_2H_5 \longrightarrow C_6H_5-C=\underset{\backslash\quad/}{C}-C_6H_5$$

(carbene from diazoacetic ester)

$$CH$$

$$|$$

$$COOC_2H_5$$

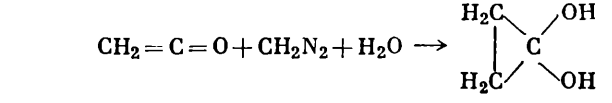
Cyclobutadiene in the solid state is unknown. It was obtained by Nenitzescu by the action of lithium amalgam on tetrabromocyclobutane and isolated in the form of a π-complex with silver nitrate:

$$BrHC\begin{array}{c}CHBr\\|\quad|\\-\quad-\end{array}CHBr \xrightarrow{Li-Hg} \xrightarrow{AgNO_3} HC\begin{array}{c}CH\\\|\cdots\|\\-\quad-\end{array}CH \cdot Ag^+NO_3^-$$

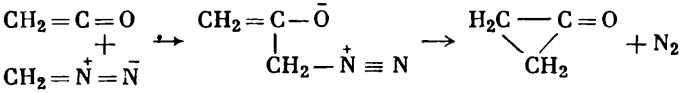
Later, other π-complexes of cyclobutadiene were obtained (see Volume IV, "Organoelement Compounds").

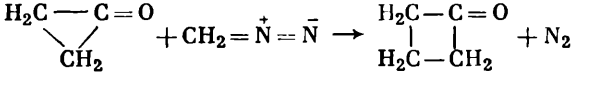
C. Carbonyl Compounds of the Cyclopropane and Cyclobutane Series

Cyclopropanone has not evidently been prepared in the pure state. The interaction of diazomethane, water and ketene gives cyclopropanone hydrate which is unstable and is readily isomerized into propionic acid:



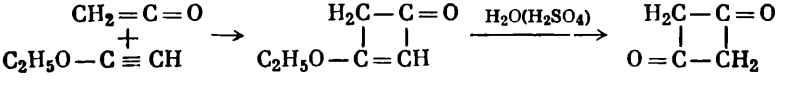
It is believed that the synthesis of **cyclobutanone** from ketene proceeds through the stage of formation of cyclopropanone:





Cyclobutanone is a liquid which boils at 99°C.

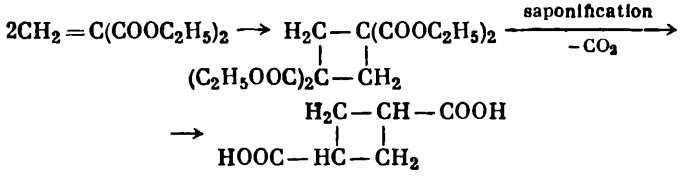
1,3-Cyclobutanedione which was first described in 1912 by H. H. Wasserman and E. V. Dehmlov was obtained as follows:



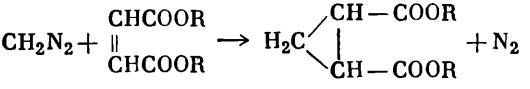
This diketone has the form of colourless plates with m.p. 119-120°C and is noticeably enolized. It gives a colouration with an aqueous solution of $FeCl_3$; it has rather strong acidic properties (pK_a about 3).

D. Carboxylic Acids of the Cyclopropane and Cyclobutane Series

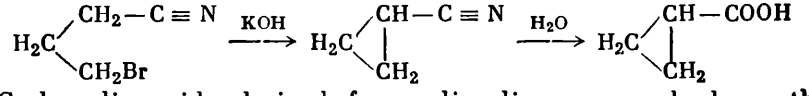
These acids are prepared in numerous syntheses of the cyclopropane and cyclobutane rings, for example, in the malonic ester synthesis (page 224). The dimerization of certain α,β-unsaturated acids yields cyclobutanecarboxylic acids; for example,



The action of diazoacetic ester (page 170) on acetylenic compounds or of diazomethane on esters of maleic acid yields cyclopropanecarboxylic acids:



Cyclopropanecarboxylic acid can also be obtained by the action of potassium hydroxide on the nitrile of γ-bromobutyric acid:



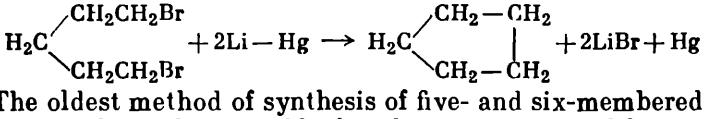
Carboxylic acids derived from alicyclic compounds have the ordinary properties of acyclic carboxylic acids. All their functional derivatives can be prepared. On decarboxylation they form the corresponding cycloalkanes.

6.2. Five- and Six-Membered Rings

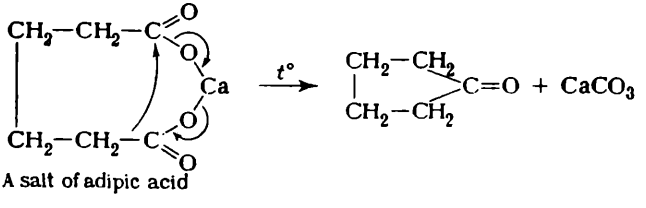
A. The Cyclopentane and Cyclohexane Series

(a) *Methods of Synthesis*

1. No methods of synthesis of five-membered rings, analogous to those for smaller rings, have been known until recently. Only in 1967 Connor and Wilson found that the action of lithium amalgam on a dioxan solution of 1,5-dibromopentane can give cyclopentane in 75 per cent yield:



2. The oldest method of synthesis of five- and six-membered cyclic ketones, which is also suitable for the preparation of larger rings, is the version of the Piria method—the pyrolysis of calcium salts of dicarboxylic acids:



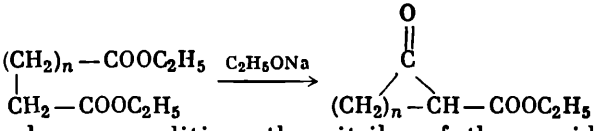
A salt of adipic acid

This method can be used to synthesize, with good yields, cyclopentanone, cyclohexanone and, with a slightly lower yield, suberone

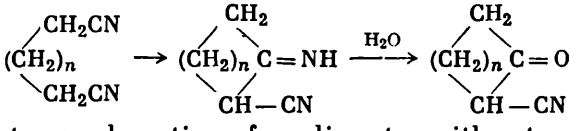
(cycloheptanone). Ketones with a larger number of atoms in the ring are produced in low yields; three- and four-membered rings cannot be prepared by this method.

Cyclopentanone and cyclohexanone are also prepared by heating dicarboxylic acids with manganese, thorium or barium oxide.

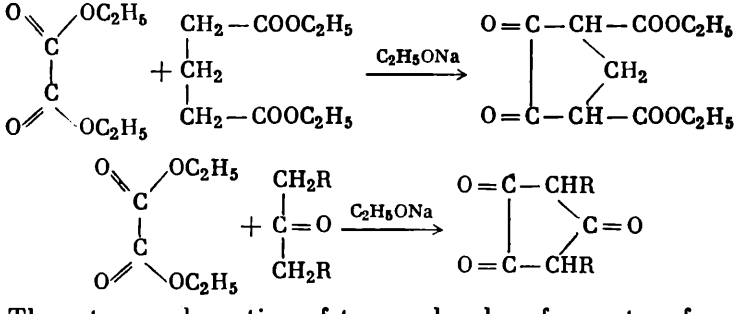
3. The ester condensation* of dicarboxylic acid esters leads to five- and six-membered cyclic β-keto acids (Dieckmann condensation):



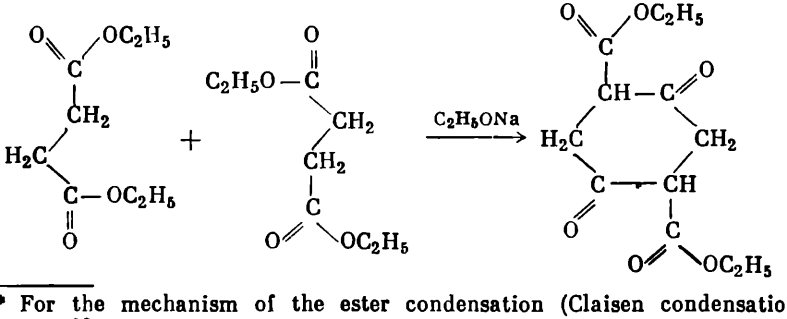
Under analogous conditions the nitriles of these acids undergo condensation (Thorpe):



4. The ester condensation of oxalic ester with esters of glutaric acid or with homologues of acetone leads to five-membered rings:

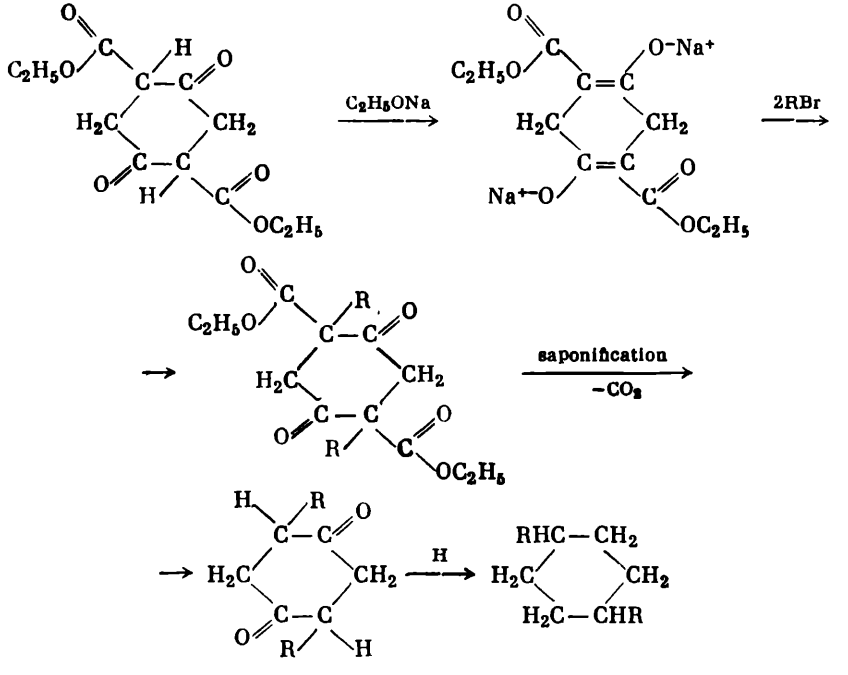


5. The ester condensation of two molecules of an ester of succinic acid gives six-membered succinylsuccinic ester:



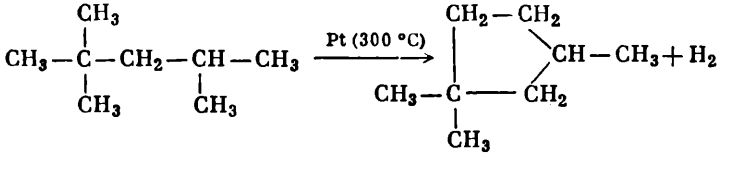
* For the mechanism of the ester condensation (Claisen condensation), see page 92.

The last three methods are especially valuable since they make it possible to prepare esters of β-ketonic acids or triketones with a 1,3-dicarbonyl grouping. All these compounds can be used in synthesis via their sodium derivatives (such as sodioacetoacetic ester or sodiumacetylacetone) to build up side chains with subsequent saponification, ketonic cleavage and, if required, reduction of the CO group to CH_2 by the Clemmensen method:



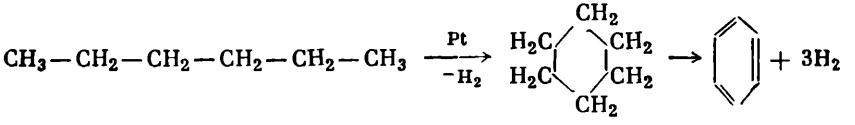
Another example of the application of method 4 is the synthesis of camphoric acid and camphor (see Volume IV, "Isoprenoids").

6. When aliphatic hydrocarbons with a chain length of 5 carbon atoms (not longer) are passed over a platinum catalyst at 300°C, the dehydrocyclization into a cyclopentane hydrocarbon takes place (B. A. Kazansky, A. L. Lieberman):

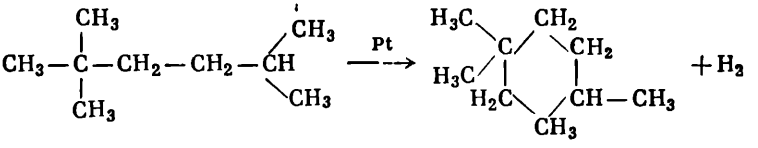


If there are more than five carbon atoms in the chain, a six-membered ring is formed, which in the absence of a quaternary atom in

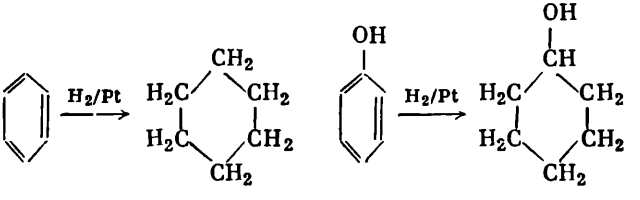
the ring is then dehydrogenated to benzene or its homologue (B. A. Kazansky, A. F. Plate):



A quaternary carbon atom prevents the aromatization:

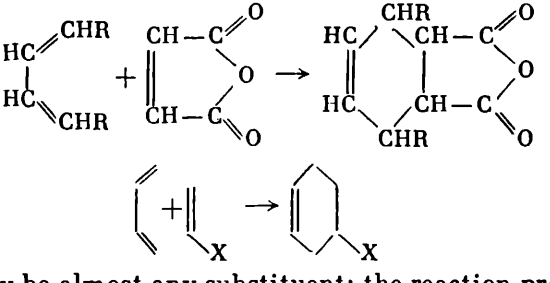


7. The principal method of synthesis of cyclohexane and its various derivatives is the catalytic hydrogenation of benzene and its derivatives over nickel, platinum or palladium:

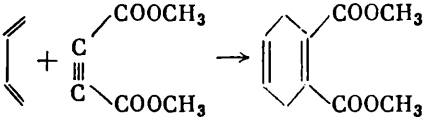


Halogen- or sulphur-containing cyclohexanes cannot be prepared in this way since these elements are replaced by hydrogen under the conditions of catalysis (Sabatier).

8. A very important method of synthesis of six-membered rings with unsaturated bonds, known since 1920, is the Diels-Alder diene synthesis:

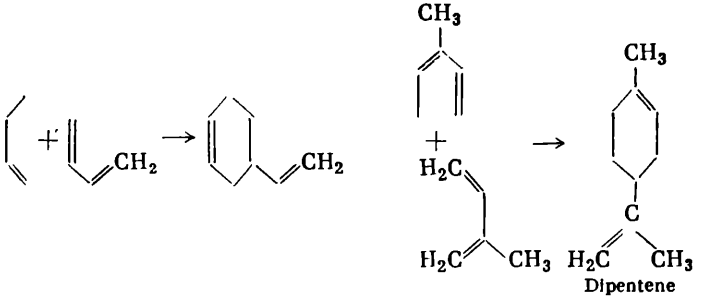


Here X may be almost any substituent; the reaction proceeds especially easily if X is an electron-attracting substituent:



The addition to a multiple bond in the Diels-Alder reaction always occurs at the *cis*-position.

The prototype of the diene synthesis is the dimerization of butadiene and isoprene by the Lebedev method (1912):



(Dipentene in the optically active form is a terpene—limonene; see Volume I, page 369.)

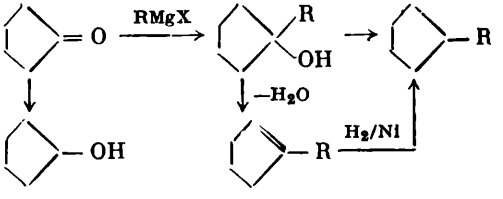
B. Cyclopentane and Its Derivatives

Petroleum contains a great variety of hydrocarbons. The investigations carried out by F. F. Beilstein, A. A. Kurbatov, V. V. Markovnikov, and N. D. Zelinsky have shown that Baku petroleum contains considerable quantities of hydrocarbons of the C_nH_{2n} series, which possess the properties of saturated compounds. These hydrocarbons were given the name of **naphthenes**. Markovnikov and Oglobin succeeded in isolating cyclopentane from petroleum. Later, Zelinsky found that the major proportion of naphthenes consists of homologues of cyclopentane and cyclohexane. The content of naphthenes varies, depending on the type of oil. Rossini (USA), beginning from 1928, investigated the composition of certain crude oils by means of physico-chemical methods and isolated about 90 individual hydrocarbons. It should be pointed out that many of the isomers of the homologues of cyclopentane and cyclohexane cannot be separated by ordinary distillation methods, even with the aid of powerful fractionating columns because their boiling points are very close to one another. Spectroscopic techniques make it possible to determine the composition of not too variegated mixtures of hydrocarbons (this, of course, has been preceded by the considerable work of isolation and study of the spectra of compounds of known structure).

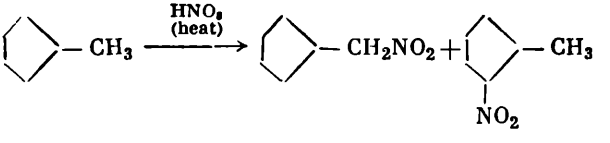
A combination method of investigating the composition of gasolines has been elaborated in this country (B. A. Kazansky, G. S. Landsberg and coworkers), which consists of the separation of gasoline into narrow fractions (cuts) by means of thorough fractionation, followed by chromatography and dehydrogenation over platinum; the narrow fractions of hydrocarbons thus obtained are then studied

with the aid of combination scattering spectra. Gas-liquid chromatography has achieved prominence as a method of investigation of such mixtures in recent years.

The derivatives of cyclopentane are synthetically most simply prepared from cyclopentanone which is obtained in good yield by calcination of the calcium salt of adipic acid or by the ester condensation of its esters (Dieckmann condensation). An alternative way is to convert cyclopentanone into cyclopentanol or into the homologues of cyclopentene (via the Grignard reaction), which on hydrogenation gives the homologues of cyclopentane:

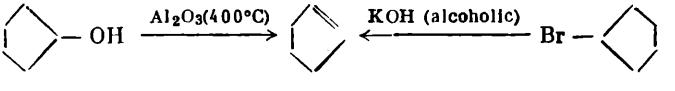


Cyclopentane and its homologues can be nitrated (by the Konovalov method); the nitration, say, of methylcyclopentane yields two products:



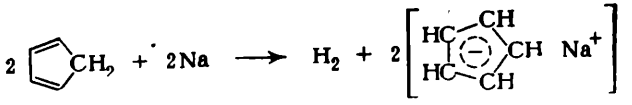
The cyclopentane ring is opened only under very severe conditions. For example, cyclopentane undergoes hydrogenation with disclosure of the ring to form pentane over platinum at 250-300°C (B. A. Kazansky and A. F. Plate).

Unsaturated compounds with a five-membered ring can be produced by conventional methods:



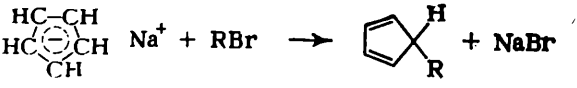
Cyclopentadiene. Cyclopentene and its homologues have the properties of ordinary unsaturated hydrocarbons. Especially interesting properties are exhibited by cyclopentadiene produced industrially from coke-oven gas, the first runnings of the crude benzene from coal tar, and from the pyrolysis products of kerosene or gasoline. A remarkable feature of cyclopentadiene is that the hydrogen atoms of its only methylene group are extremely active. One of these hydrogen atoms can be replaced by sodium; in the anion of the resulting sodium compound all the carbon atoms are equivalent and the negative charge is evenly spread, or delocalized. about these five ring

carbon atoms:

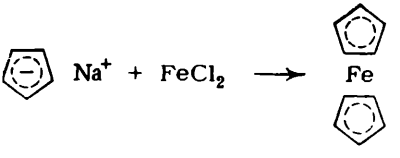


This cyclopentadienyl anion is an aromatic system in the Hückel sense (see Volume IV, "Carbanions"); it is quite stable, is not isomerized and does not expel a proton from solvents such as ether or tetrahydrofuran.

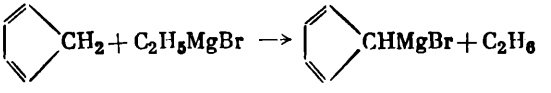
The action of alkyl halides on cyclopentadienylsodium can give homologues of cyclopentadiene:



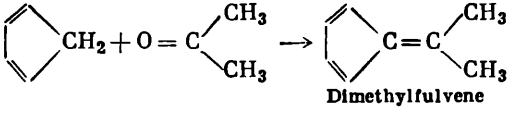
The reaction between the chlorides of many metals and cyclopentadienylsodium yields organometallic compounds of the **ferrocene** type*:



The organomagnesium compound of cyclopentadiene is prepared by the treatment of cyclopentadiene with alkylmagnesium halides:



The mobility of the methylene hydrogens in cyclopentadiene is also exhibited in its facile condensation with aldehydes and ketones:



Dimethylfulvene

The thus obtained **fulvenes** are unsaturated coloured hydrocarbons with a high dipole moment (about 1.5 D).

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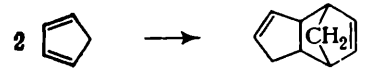
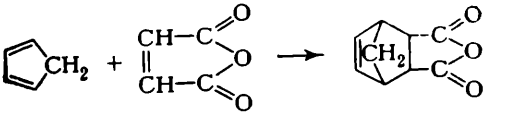
* For more detail, see Volume IV, "Non-Benzenoid Aromatic Systems".

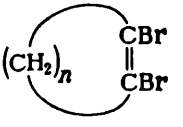
Cyclopentadiene readily dimerizes into **dicyclopentadiene:**



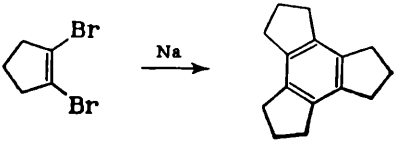
and enters readily into reactions typical of dienes, say, the Diels-Alder reaction:



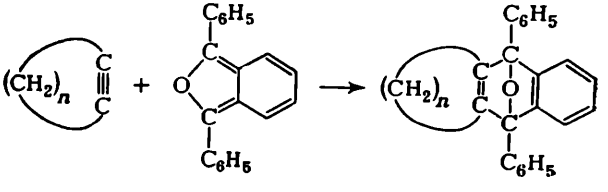
A. E. Favorsky who studied, beginning from 1912, the possibility of introducing a triple bond into medium-sized rings and made use, for this purpose, of the action of sodium on dibromides of the type



instead of a cycloalkyne, obtained, as a result of his work with M. F. Shostakovsky, a trimer—a derivative of benzene:



In addition to the trimer, a polymer was obtained, probably the polymer of cyclopentadiene. Wittig succeeded, however, in isolating the transiently formed cycloalkyne by eliminating bromine from the Favorsky dibromides with $n = 3$, 4 and 5 by the action of magnesium in the presence of a very active diene. **Diphenylisobenzofuran** was found to be a highly active diene. It enters into reaction with the very short-lived transiently existing cycloalkyne (in the experiments carried out by Favorsky, the cycloalkyne trimerized into a benzene derivative):

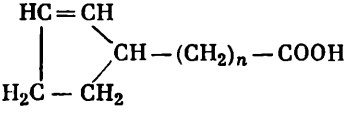


The reaction proves the transient existence of cyclopentyne, cyclohexyne and cycloheptyne. Cyclooctyne is more stable, though still very reactive. It was prepared by Blomquist.

C. Carboxylic Acids of the Cyclopentane Series

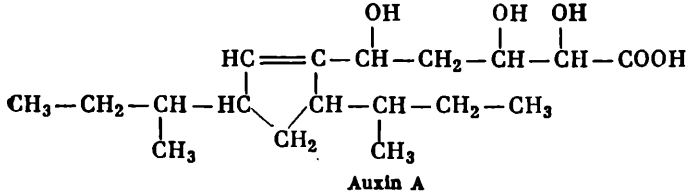
Along with the acids of the cyclohexane series, cyclopentanecarboxylic acids enter into the composition of so-called **naphthenic acids** isolated from petroleum. This mixture has been found to contain, in particular, cyclopentanecarboxylic, 1,2,2-trimethylcyclopentanecarboxylic and other acids. The fields of application of naphthenic acids are varied. Their copper and manganese salts are used in the paint-and-varnish industry as desiccants—initiators of oxidation and polymerization of drying oils; the copper salt is a good fungicide; some of the salts of naphthenic acids find use as insecticides and emulsifying agents.

The essential oils of certain tropical plants contain **hydnocarpic** acid ($n = 10$) and **chaulmoogric** acid ($n = 12$), both having a cyclopentene ring:

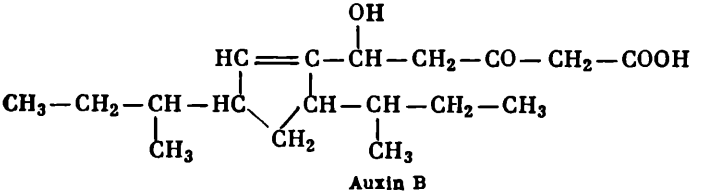


The vegetable oils—hydnocarpic and chaulmoogra oils—have long been used in the East as a nature remedy in the treatment of leprosy.

A five-membered ring is also contained in the structure of important natural substances called **auxins:**



Auxin A



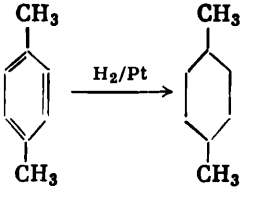
Auxin B

Auxins are present in the tips of growing plants (and in the green plant shoots) and stimulate plant growth (Kögl).

D. Cyclohexane and Its Derivatives

Compounds containing six-membered alicycles in their structure are among the most widespread in the organic world. The corresponding cyclic groupings of atoms are contained in the majority of terpenes, steroids, and alkaloids. Often encountered among the derivatives of cyclohexane are bridged-ring compounds and compounds with fused rings. These types of compounds will be discussed in Volume IV ("Isoprenoids"). Cyclohexane and its homologues are contained in considerable amounts in gasolines, especially in those entering into the composition of Caucasian petroleums.

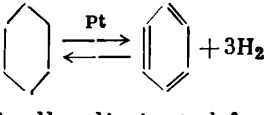
The derivatives of cyclohexane are mainly prepared by the hydrogenation of aromatic compounds over platinum or nickel (Sabatier):



Cyclohexane itself is produced by the hydrogenation of benzene.

Cyclohexane and its homologues, like the homologues of cycloheptane, enter into reactions characteristic of paraffins: they are capable of being halogenated, nitrated, and sulphochlorinated by a homolytic mechanism. The cyclohexane ring is quite stable towards oxidation and hydrogenation. The oxygen-containing derivatives of cyclohexane—cyclohexanone and cyclohexanol—are oxidized much more easily.

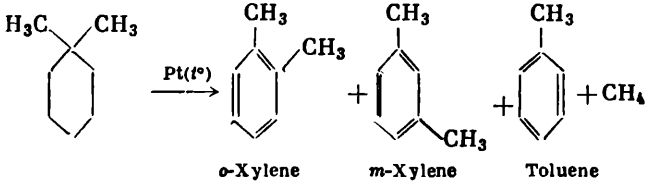
Dehydrogenation of Cyclohexane. Irreversible Catalysis. The hydrogenation of the derivatives of benzene is reversible reaction, like many catalytic reactions. Under the same conditions and with the same catalysts, but in the absence of hydrogen, cyclohexane can be dehydrogenated to benzene (over platinum or palladium at about 300°C):



The hydrogen is gradually eliminated from the reaction medium, and the conversion therefore is practically quantitative.

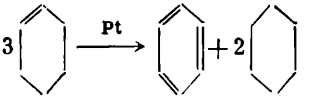
The homologues of cyclohexane can also be converted into the homologues of benzene without any change of the carbon skeleton (N. D. Zelinsky). This of course does not apply to 1,1-dimethylcyclohexane and other *gem*-substituted cyclohexanes. Their dehydrogenation takes place under considerably more severe conditions and is

accompanied by the elimination of one of the alkyl groups or by isomerization. For example, from 1,1-dimethylcyclohexane there is obtained a mixture of *ortho*- and *meta*-xylenes, toluene and methane (B. A. Kazansky, A. L. Lieberman):



Cyclohexene and cyclohexadienes are hydrogenated in approximately the same way as ordinary unsaturated compounds. The ease of their dehydrogenation is accounted for by the fact that this reaction involves the formation of the energetically favourable aromatic system of benzene.

Interesting in this connection is the tendency of cyclohexene towards **disproportionation.** In the presence of platinum or palladium as catalyst, cyclohexene even at room temperature disproportionates to benzene and cyclohexane as a result of an exothermic reaction:



This reaction was called the **irreversible catalysis** by Zelinsky because the reversible reaction is not feasible—neither cyclohexene nor cyclohexadiene can be obtained from a mixture of benzene and cyclohexane. The reaction probably consists of the dehydrogenation of cyclohexene, the hydrogen evolved hydrogenating the unreacted cyclohexene.

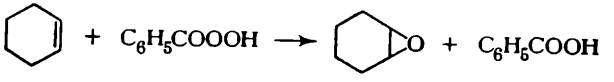
The dehydrogenation of the homologues of cyclohexene, i.e., their conversion into the homologues of benzene, is used for the elucidation of their structure.

E. Unsaturated Compounds of the Cyclohexane Series

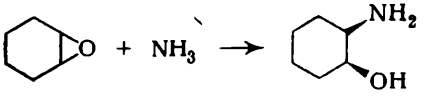
Cyclohexene is prepared by the catalytic dehydration of cyclohexanol, its vapours being passed over aluminium oxide at 350-400°C. Sulphuric or phosphoric acid may also be employed as dehydrating agents.

Cyclohexene possesses all the ordinary properties of unsaturated compounds: it adds on halogens, renders the potassium permanganate

solution colourless, and when acted on by peracids forms **cyclohexene oxide**



It is interesting that cyclohexene oxide reacts with nucleophilic reagents, for example, with amines



with *trans*-disclosure of the epoxide ring, i.e., with a Walden inversion at the carbon atom being attacked. In this process, both substituents are initially in the axial position (the axial ring-opening). This rule is important for the elucidation of the mutual disposition of substituents in the rigidly built systems of the cyclohexane type, say, in steroids.

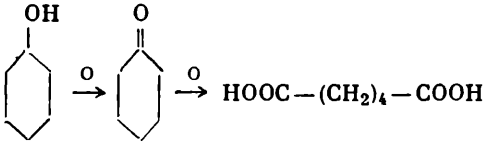
Cyclohexadiene is a typical diene with a conjugated bond system. It enters into reactions of diene synthesis and other reactions.

The hydrogenation and dehydrogenation of cyclohexane and cyclohexene has already been discussed.

F. Alcohols of the Cyclohexane Series

Cyclohexanol is prepared by the catalytic hydrogenation of phenol. It can also be made by the reduction of cyclohexanone and by other general methods.

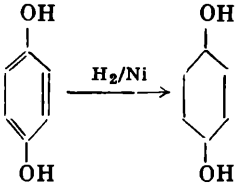
Cyclohexanol when oxidized gives cyclohexanone which can be oxidized further to adipic acid:



Cyclohexanol is the intermediate product in the production of caprolactam and adipic acid (hence, of Nylon 6 and Nylon 6,6).

Cyclohexanediols are prepared by the hydrogenation of the corresponding aromatic compounds—phenols. For example, the diol **quini-**

tol is obtained by the hydrogenation of hydroquinone:

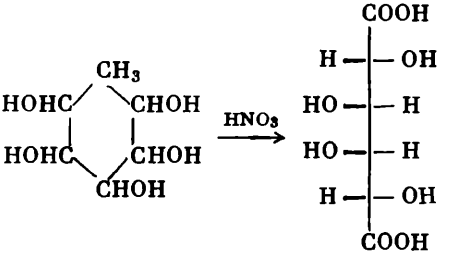


Quinitol

The *cis*- and *trans*-isomers of quinitol are known to exist.

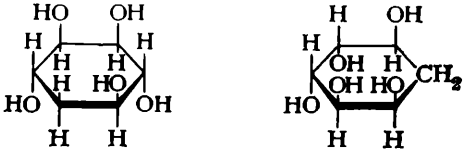
Quercitol, whose molecule contains five hydroxyls, is also called **acorn sugar** since it is found in acorns and has a sweet taste. The sweet taste is characteristic of the majority of alcohols with several hydroxyl groups.

The oxidation of quercitol by nitric acid gives mucic acid, whose configuration is known:



Mucic acid

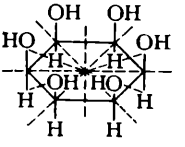
Hence, quercitol which is optically active should be assigned one of the following formulas in which the configurations of the four asymmetric centres coincide with those of the four centres in mucic acid:

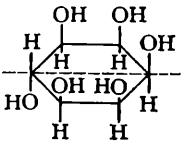


It is the formula on the left that has been found to correspond to quercitol.

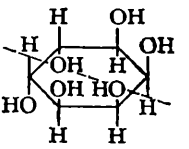
Inositols (*hexahydroxycyclohexanes*) are the stereoisomers of cyclohexanehexols (eight geometric isomers one of which can be resolved into optical antipodes).

Except D- and L-inositols, all the stereoisomers have at least one plane of symmetry designated by dashed lines in the formulas given below. The molecules of D- and L-inositols are built asymmetrically.

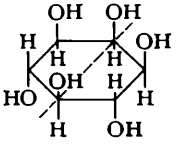




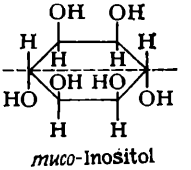
epi-Inositol



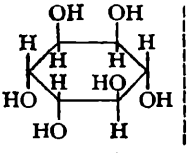
allo-Inositol



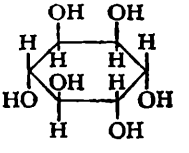
meso-Inositol



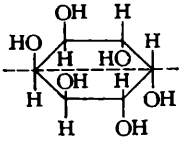
muco-Inositol

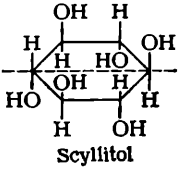


L-Inositol



D-Inositol

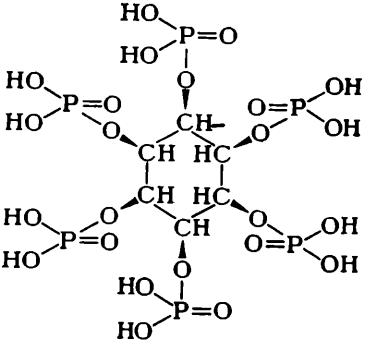




Scyllitol

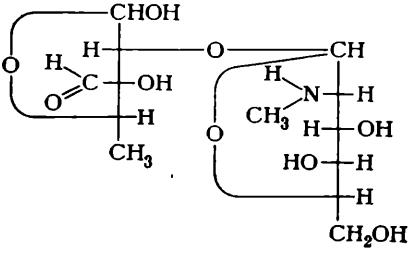
meso-**Inositol** (*myo*-**inositol**) is widely distributed in the plant and animal kingdom. It is contained, in the free state or in the form of derivatives, in the muscles and in the various organs of animals, in the seeds of plants, etc. *meso*-Inositol is a component of "bios", the growth-stimulating factor for certain microorganisms (yeast) and is known as bios-1 (Kögl). Some plants contain also D- and L-inositols (their monomethyl ethers).

Widely distributed in plants is **phytin** which is the phosphorate ester of *meso*-inositol

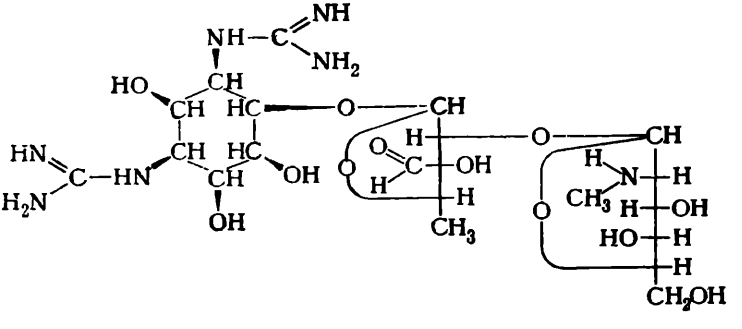


and is found as the magnesium, calcium or potassium salts. Phytin is used medicinally as a nutrient for rickets, anemia, and tuberculosis.

In 1944, Waksman isolated **streptomycin**, a highly important antibiotic, from the fungi of *Streptomyces griseus*. It is widely used in the treatment of tuberculosis and to combat diseases invoked by streptococci and staphylococci. The acid hydrolysis of streptomycin leads to the splitting of its molecule, $C_{21}H_{39}N_7O_{12}$, into two parts: **streptidine** (a diguanidino derivative), $C_8H_{18}N_6O_4$, the basis of which is the cyclohexane ring, and a disaccharide, **streptobiosamine**, $C_{13}H_{23}NO_9$, which is then hydrolysed to two monosaccharides (in one of which the α-hydroxyl is replaced by a methylamino group). The ordinary determination of the structure and configuration of carbohydrates reveals the following formula for streptobiosamine:



The cyclohexane part of the molecule (streptidine) contains four secondary-alcoholic hydroxyls and two guanidine residues. One of the hydroxyls is united to streptobiosamine through a glycosidic linkage, so that the entire structure of streptomycin is as follows (Folkers):

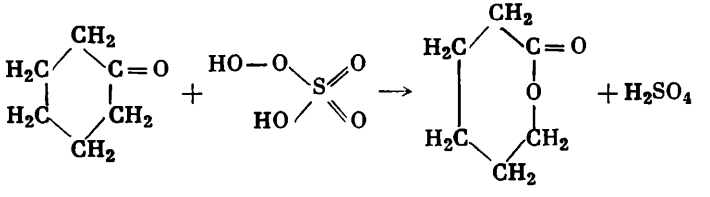


G. Ketones of the Cyclohexane Series

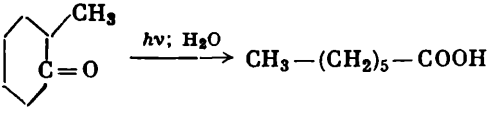
Cyclohexanone is prepared by the oxidation of cyclohexanol or by the catalytic oxidation of cyclohexane itself. It is an important solvent and an intermediate in one of the syntheses of caprolactam. The older method of preparing cyclohexanone is the pyrolysis of the

calcium salt of pimelic acid (Piria), for which reason it is also known as **pimelic ketone.** The chemical properties of cyclohexanone are similar to those of aliphatic ketones.

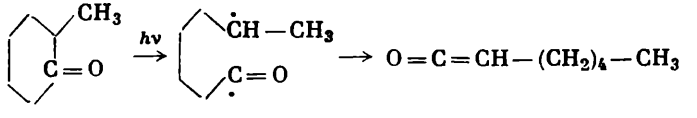
On oxidation by HNO_3, $KMnO_4$, or $H_2Cr_2O_7$, cyclohexanone forms, in good yield, adipic acid (the usual route for preparation of adipic acid). The oxidation with Caro's acid (permonosulphuric acid) leads to caprolactone (Baeyer and Villiger):



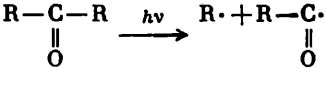
Under the influence of light cyclic ketones are opened and give, in the presence of water, monobasic fatty acids (Ciamician): cyclohexanone gives caproic acid, $CH_3—(CH_2)_4—COOH$, and methylcyclohexanone forms enanthic acid:



In analogous reactions proceeding in the absence of water, the formation of a ketene is revealed by infrared spectroscopy, from which it may be concluded that the mechanism of this reaction involves the stages depicted by the following scheme:

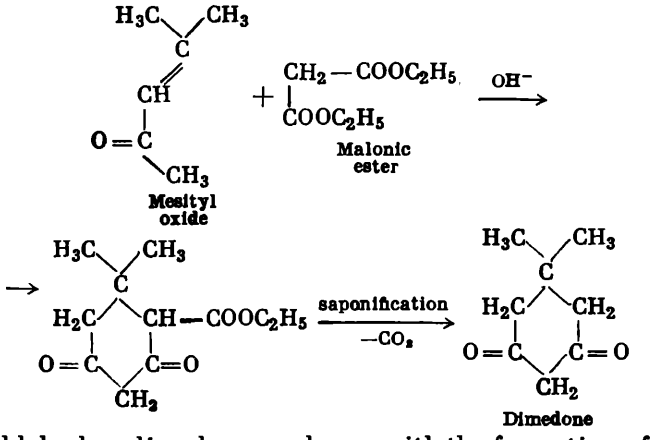


Let us recall that the photolysis of fatty ketones occurs in the following way:

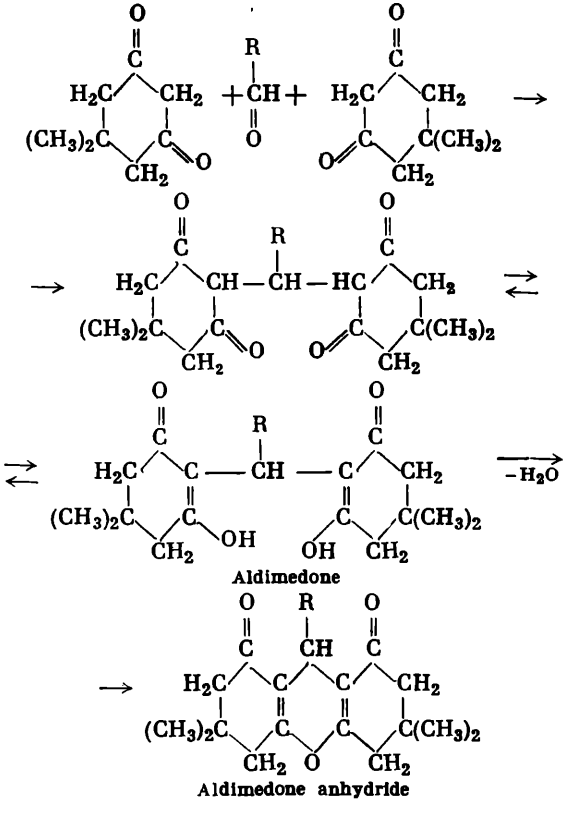


Cyclohexanone contains, in equilibrium at 25°C, by two orders of magnitude more tautomeric enol form than acetone, namely, by 0.02 per cent.

1,1-Dimethyl-3,5-cyclohexanedione (*dimedone* or *methone*), which is used as a reagent for the discovery and identification of aldehydes, is made by the condensation of malonic ester and mesityl oxide by the Michael reaction:



With aldehydes, dimedone condenses with the formation of crystalline high-melting products—**aldimedone** or, under more drastic conditions, aldimedone anhydride:

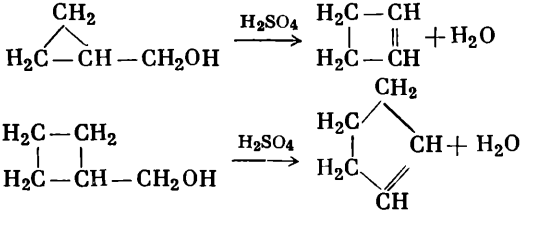


These compounds have a high molecular weight, high melting points and crystallize well and are therefore very convenient for the identification of aldehydes.

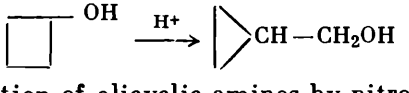
6.3. Interconversion of Rings

Cyclic halogen derivatives, alcohols, amines, carbonyl compounds can be isomerized with the extension or compression of the ring. Many reactions of cyclic compounds involve a change of the ring size. The greatest tendency towards extension is exhibited by three- and four-membered rings. Ring extension occurs in such a way that one of the atoms of the side chain enters into the ring; ring compression (or contraction) is accompanied by the migration of one of the ring carbon atoms to the side chain. Rearrangements of this kind* have been thoroughly studied by N. Ya. Demyanov and N. M. Kishner.

1. The dehydration of alcohols of the alicyclic series is often accompanied by a rearrangement. If the hydroxyl group is in a side chain at an α-carbon atom, the ring is extended, especially readily in the case of alcohols of the cyclopropane and cyclobutane series. The catalysts used are strong hydrogen or Lewis acids (zinc chloride, aluminium chloride):



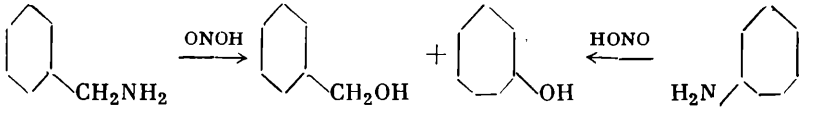
The dehydration of cyclohexanol and cyclopentanol is accompanied in some cases by ring compression. Under the action of acids, cyclobutanol can be partly converted into cyclopropylcarbinol:



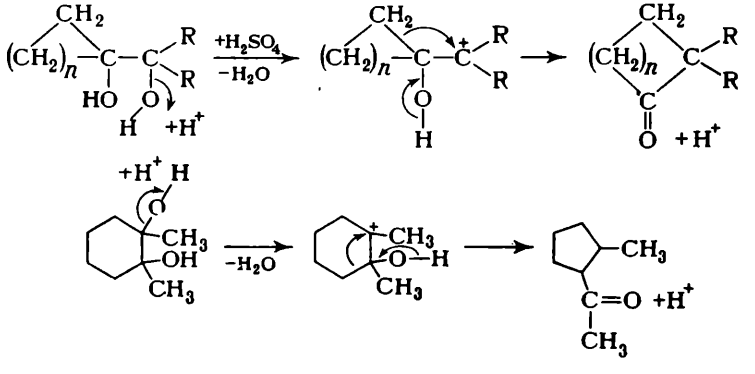
2. The deamination of alicyclic amines by nitrous acid also leads to alicyclic alcohols with rings of a larger or smaller size. As an example, aminomethylcyclohexane gives under these conditions a mixture of cycloheptyl alcohol and cyclohexylcarbinol and dehydration products. The same products are obtained by the action of nit-

* For a more detailed discussion of the mechanism of these rearrangements, see Volume IV, "Rearrangements".

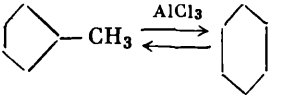
rous acid on cycloheptylamine (Demyanov):



3. The pinacol-pinacoline rearrangement of cycloalkanes may involve either the contraction or extension of the ring. The mechanism of this rearrangement is the same as in the aliphatic series: protonation takes place, one of the hydroxyls is eliminated as water, and one of the radicals complete with its two bonding electrons migrates to the neighbouring carbon atom that has become positively charged in the process. In the case of cyclic compounds, such a radical is one of the ring linkages:



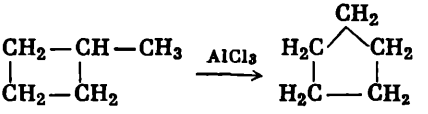
4. On heating with aluminium chloride an equilibrium isomerization is set up between the hydrocarbons of the cyclopentane and cyclohexane series (N. D. Zelinsky, O. Aschan, K. Nenitzescu). For example,



The mixture obtained contains methylcyclopentane and cyclohexane; the equilibrium sets in at temperatures of 70-80°C with the relative concentration ratio of cyclohexane and methylcyclopentane being equal to 3 : 1. From this it follows that the cyclopentane and cyclohexane rings are rather close to each other in thermodynamic stability.

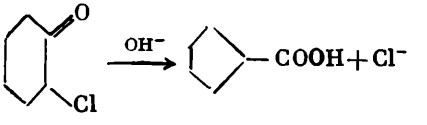
Under the influence of the same catalyst the homologues of cyclobutane are irreversibly converted into the homologues of cyclopen-

tane (M. B. Turova-Pollak). For example,



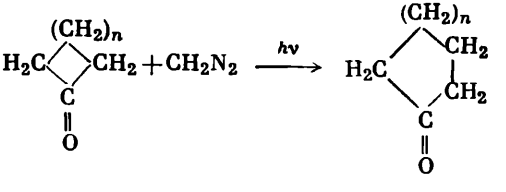
Cycloheptane isomerizes under these conditions with contraction of the ring.

5. Ring compression by the Favorsky rearrangement. Cyclic α-chloroketones undergo, under the action of alkali, a Favorsky rearrangement, being smoothly converted into cycloalkanecarboxylic acids with a ring containing one link less:

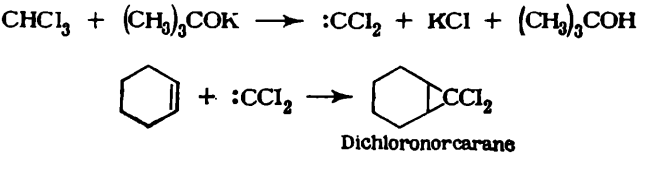


The mechanism of the rearrangement will be discussed in Volume IV under "Rearrangements". The use of this reaction in the building-up of the tetracyclic bridged-ring compound cubane will be considered in Sec. 6.6.

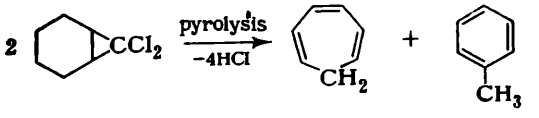
6. Ring extension with the aid of carbenes. When diazomethane is photochemically decomposed in the presence of cyclic ketones, the resulting carbene $:CH_2$ (see Sec. 6.5. B and Volume IV, "Carbenes") is inserted between the carbonyl carbon atom and the adjacent ring atom:



Dichlorocarbene adds on smoothly to the double bond of cyclohexene:



The resulting dichlorbnorcarane can be isomerized pyrolytically to the derivatives of cycloheptane:

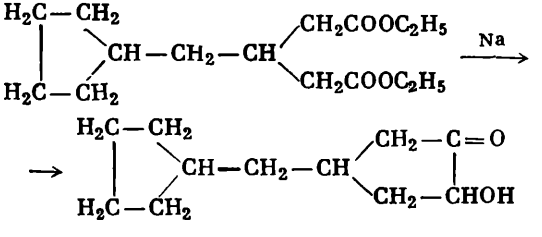


6.4. Alicyclic Compounds with Two or More Rings

A. Bicyclic Compounds with Isolated Rings

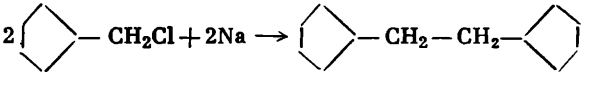
Here we shall deal with compounds of two classes which are similar to each other in properties and methods of preparation: alicycles, whose rings are separated by a chain of atoms, and those with rings connected by one bond only.

These compounds can be prepared by the methods employed for the preparation of monocyclic compounds. It is simpler to start with compounds in which one ring is already present in the molecule by using, say, the method of acyloin condensation (see Sec. 6.5.A):

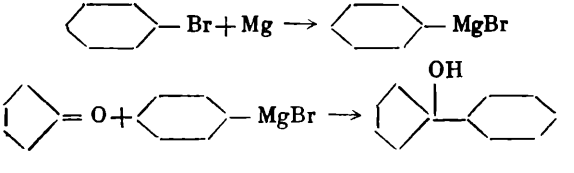


They can also be produced by the condensation of two molecules each of which contains a ring, by the following routes.

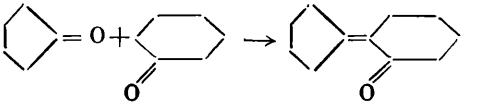
1. The Wurtz reaction:



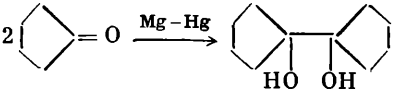
2. With the aid of organomagnesium compounds:



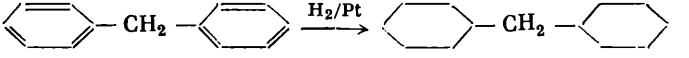
3. The condensation of cyclic aldehydes, ketones, etc.:



4. The reduction of ketones (preparation of cyclic pinacols):



5. The hydrogenation of the corresponding aromatic compounds:

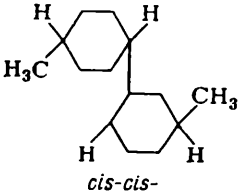


and by many other methods.

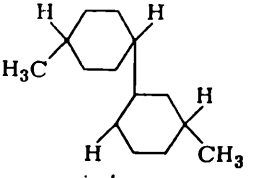
The properties of bicyclic compounds with isolated rings do not practically differ from those of monocyclic compounds.

Important natural compounds of this class (with two isolated cyclic groupings in the molecule) are many of the carotenoids (see Volume IV under "Isoprenoids").

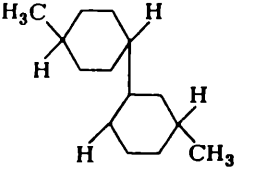
Bicyclic compounds, whose rings are joined by a single carbon-carbon bond, display a new kind of stereoisomerism. For example, 4,4′-dimethyldicyclohexyl exists in the form of three stereoisomers (for simplicity, the cyclohexane rings are depicted flat):



cis-cis-

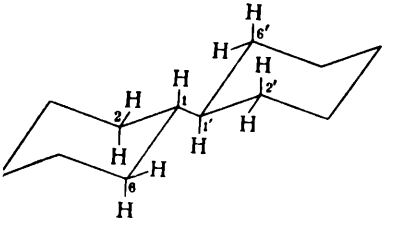


cis-trans-



trans-trans-

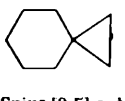
Such stereoisomerism is accounted for by the fact that (at ordinary temperatures) the rings cannot be rotated relative to each other. In such a rotation, a position must set in when the methylene groups of two rings in 2,2′ and 6,6′ positions will be at small distances from each other and the further rotation becomes impossible:



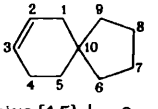
The 2,2′- or 3,3′-disubstituted dicyclohexyls have even more stereoisomers. Of the six geometric stereoisomers of 2,2′-dimethyldicyclohexyl, four exist as optically active forms. Thus, the total number of stereoisomers in this case is 10.

B. Spirans

Spirans or spiro compounds are bicyclic structures in which two ring systems share one common atom. These compounds are named systematically by using the word *spiro* as a prefix; immediately after spiro are placed numerals denoting the number of carbon atoms (excepting the carbon atom common to both rings, which is called the spiro atom) in each ring; these numbers start with the lower and are separated by a full stop (period) and placed in square brackets; then, if there are no substituents in the rings, the numerals in square brackets are followed by the name of the corresponding hydrocarbon (nonane, decane, etc.) with the same total number of carbon atoms as in the rings. For example,

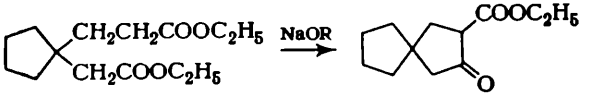


Spiro [2.5] octane

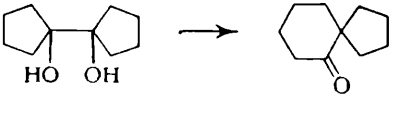


Spiro [4.5] dec-2-ene

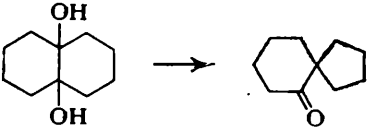
Spirans can be prepared by ordinary methods of cyclization; for example,



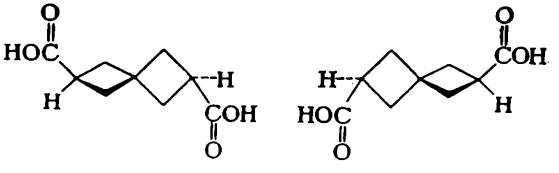
Compression or extension of the rings of certain bicyclic compounds may also lead to spirans. This takes place, for example, in the pinacol-pinacoline rearrangement of dicyclopentyl-1,1′-diol (N. D. Zelinsky, N. I. Shuikin):



Another example of pinacol rearrangement accompanied by the ring compression is the following:



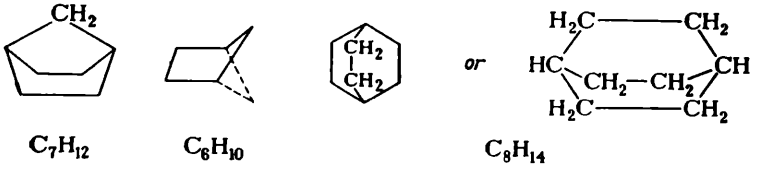
Spiro compounds are characterized by a special kind of stereoisomerism. For example, spiro[3.3]heptane-2,5-dicarboxylic acid exists as two optical antipodes in spite of the absence of asymmetric carbon atoms. This is attributed to the asymmetry of the molecule as a whole. The rings of the molecule of spiro[3.3]heptane are arranged in mutually perpendicular planes. The molecule of the acid mentioned above cannot therefore be superimposed on its mirror image:



Spiro compounds are, as a rule, less stable than ordinary alicyclic compounds. Their rings (small) are more readily opened under the action of strong acids, chlorine, bromine, etc.

C. Alicyclic Compounds with Fused Rings

It should be noted in the first place that in the case of polycyclic fused-ring compounds there may arise confusion as regards the number of rings. For example, the following alicyclic compounds



C_7H_{12} C_6H_{10} C_8H_{14}

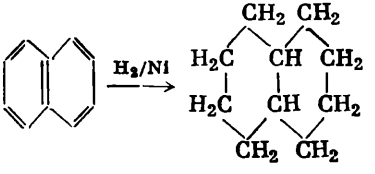
may be mistaken for tricyclic compounds. It should be remembered that saturated (i.e., having no π-bonds) monoalicyclic hydrocarbons have a general formula of C_nH_{2n}; bicyclic, C_nH_{2n-2}; tricyclic, C_nH_{2n-4}, etc.

All the hydrocarbons shown above are bicyclic compounds.

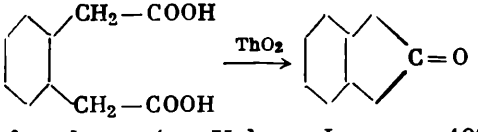
(a) *Methods of Synthesis*

The following methods are suitable for preparation of alicyclic fused-ring compounds.

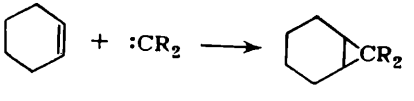
1. The catalytic hydrogenation of condensed aromatic systems such as naphthalene for bicyclic compounds, anthracene or phenanthrene for tricyclic compounds (see Volume III):



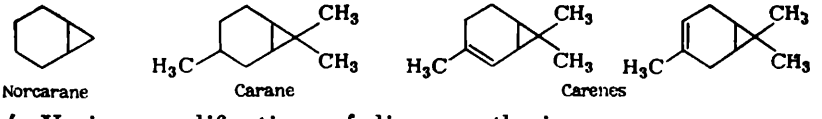
2. Cyclization by one of the methods described in Sec. 6.2 but starting with compounds containing one ring. For instance,



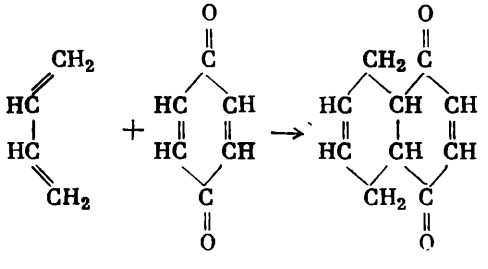
3. Addition of carbenes (see Volume I, pages 107 and 298 and Volume IV, "Carbenes") to unsaturated monocyclic compounds:



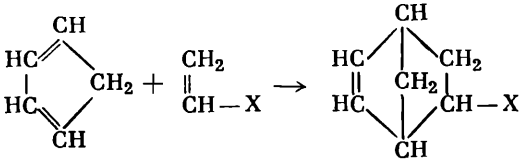
If R=H in the given example, bicyclo [1.4.0]heptane is obtained, which is called **norcarane**. Carane itself, $C_{10}H_{18}$, which has the same bicyclic system, is the parent hydrocarbon of carenes, $C_{10}H_{16}$, discovered in the turpentine oil of the Russian pine (B. A. Arbuzov):



4. Various modifications of diene synthesis:

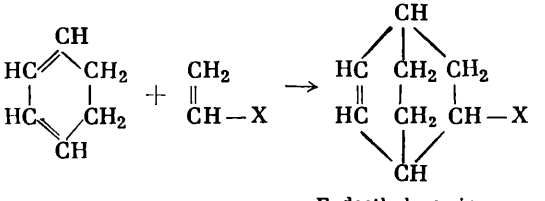


(1)



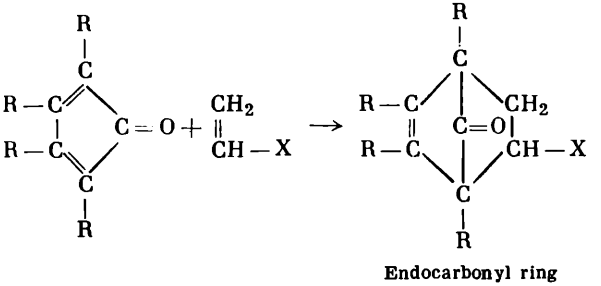
(2)

Endomethylene ring



(3)

Endoethylene ring



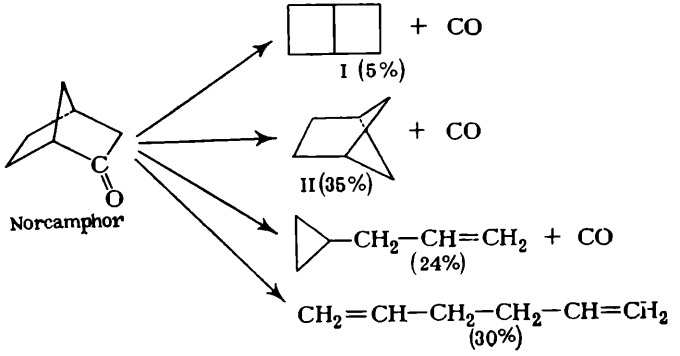
(4)

Endocarbonyl ring

The hydrogenation of the endomethylene compound shown above gives **norcamphane** (if X = halogen, it is replaced on hydrogenation by H). This is bicyclo[2.2.1]heptane, which has the skeleton of camphor, borneol and other terpenoids (see Volume IV, "Isoprenoids"). The dehydrogenation of endoethylene compounds proceeds with the splitting-off of ethylene and leads to derivatives of benzene.

5. Isolation from naturally occurring compounds (see Volume IV, "Isoprenoids").

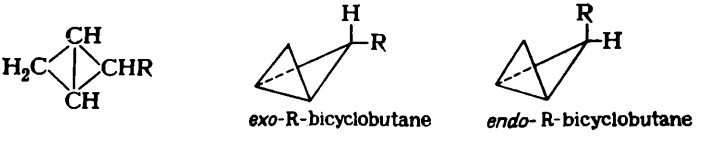
6. Finally, use may be made of the photosensibilized (with mercury vapour) decomposition of bicyclic ketones. For example, norcamphor under these conditions gives, among other decomposition products, bicyclo[2.2.0]hexane (I) and bicyclo[2.1.1]hexane (II) (Srinivasan):



Bicyclo[3.2.0]heptan-3-one under these conditions forms the same bicyclo[2.2.0]hexane (I), but the yield does not exceed 5 per cent. The compound obtained boils at 90°C (Kromer, Srinivasan).

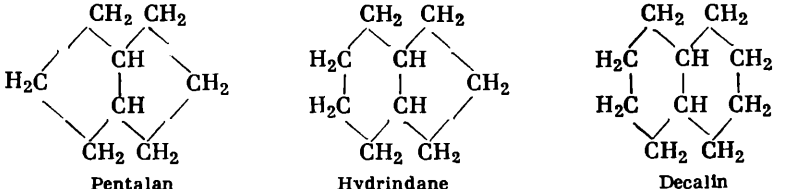
XXII. Stereochemistry

The stereochemistry of alicyclic fused-ring (or condensed-ring) systems is rather complicated. This is associated with the spatial disposition of the skeleton, its relative rigidity and the low symmetry of molecules. Monosubstituted bicyclo[1.1.0]butanes are represented by two geometrical isomers*:



exo-R-bicyclobutane *endo*-R-bicyclobutane

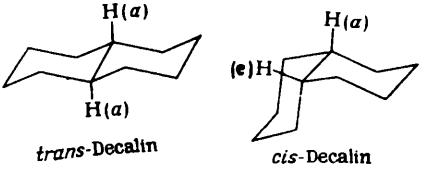
Fused-ring systems with a larger number of ring atoms may exist by themselves, even without substituents, in the form of two isomers. For example, pentalan, hydrindane and decalin are each represented by a pair of geometrical isomers.



Pentalan (bicyclo[3.3.0]octane) Hydrindane (bicyclo[3.4.0]nonane) Decalin (bicyclo[4.4.0]decane)

* The prefix *endo-* indicates that the substituent is facing the inside (convex side) of the molecule. The stereochemically related isomer is given the prefix *exo-*.

Let us consider in more detail the isomerism of decalin predicted in 1918 by Mohr and proved in 1925 by W. Hückel who separated, through fractional distillation, a mixture of decalins resulting from the hydrogenation of naphthalene and isolated *trans*-decalin (b.p. 185°C) and *cis*-decalin (b.p. 194°C). One can visualize two models in which the chair conformations of cyclohexane are condensed with each other. In model *A* the angular hydrogen atoms (at the key atoms of the molecule) are situated on opposite sides of the fused-ring system (*trans*-decalin); in *cis*-decalin (model *B*) they are on the same side of the molecule:



trans-Decalin — *cis*-Decalin

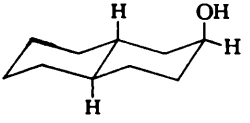
A *B*

These models cannot be converted into each other by rotation about single carbon-carbon bonds and are isomers and not different conformations of a single compound. Both *cis*- and *trans*-decalins may assume several conformations; here only the most favourable conformations of each of the isomers are shown, namely, the chair-chair conformation (Hassel, 1946).

If one of the rings of decalin is regarded as a disubstituted cyclohexane (the substituents are the carbon atoms of the other ring), then in *trans*-decalin these substituents are both equatorial, while the angular hydrogen atoms are axial. In *cis*-decalin the fusion of the rings is equatorial-axial, and one of the angular hydrogens is axial and the other equatorial. It has already been pointed out that the diequatorial disposition of the substituents in cyclohexane is more stable. From this point of view *trans*-decalin must have a lower energy content. The same conclusion can be arrived at if we estimate the energies of two isomers in terms of the heats of combustion, as has been done for cyclohexane (page 211).

The different nature of the bonds in decalins is responsible for some other differences as well. The diequatorial fusion of the rings in *trans*-decalin renders its molecule relatively rigid. Indeed, though each ring of *trans*-decalin can adopt the boat conformation, complete conversion of the molecule into a new chair conformation is impossible because the equatorial bonds at tertiary carbon atoms cannot become axial. This is understandable: no ring can be built with the participation of two neighbouring axial bonds directed to opposite sides at an angle of 180°. The angular hydrogens of *trans*-decalin can be only axial. If the β- (or 2-) substituent in *trans*-decalin is in the

cis-position to the nearest of these hydrogens, it can also be only axial; and if in the *trans*-position, only equatorial. For example, *trans*-2-decalol is represented by two geometrical isomers; in one of them the hydroxyl group is axial (a) and in the other, equatorial (e):



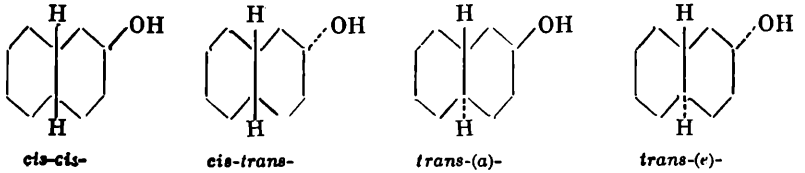
trans-(*a*)-2-Decalol *trans*-(*e*)-2-Decalol

Thus, in *trans*-decalins we deal not with the equatorial and axial conformations but with the **equatorial-axial isomerism.**

The *cis*-decalin system built by means of equatorial and axial bonds is more flexible and the interconversion of the axial and equatorial conformations of *cis*-decalin is possible. But the number of isomers remains the same since the substituent is either on the same side of the ring as the angular hydrogens (*cis-cis*-isomer) or on the opposite side (*cis-trans*-isomer).

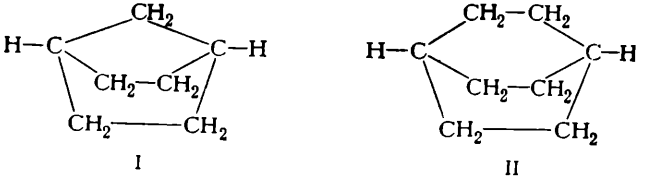
Fused-ring systems are usually represented by compact formulas in which the bonds of angular hydrogens and substituents situated below the plane of the ring are denoted by a broken line and those above the ring plane by a full line.

For example, the four possible isomers of β-decalol can be represented as follows:



cis-cis- *cis-trans*- *trans*-(*a*)- *trans*-(*e*)-

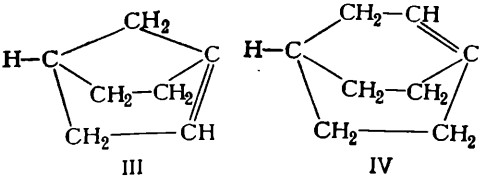
Even in the case of decalins we see that the fused-bicyclic system is much more rigid (the conformational mobility being frozen out) than monocyclic systems. This rigidness becomes even greater in systems with bridges of one or two linkages, say, in bicyclo[2.2.1]heptane (I, norcamphane) and in bicyclo[2.2.2]octane (II):



I II

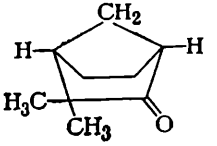
This lack of conformational mobility is reflected in the stereochemistry of such rigid rings in the following way:

1. The conformation is more or less fixed.
2. The Bredt empirical rule becomes valid for phenomena associated with the geometrical isomerism: "no double bond can be formed at the bridgehead". In other words, no systems of the type III or IV exist:



III IV

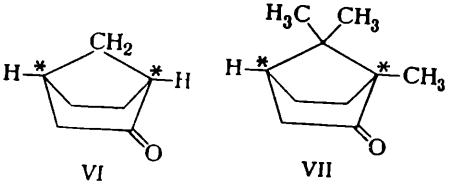
This rule can be easily ascertained from the viewpoint of the geometry of an olefinic grouping of atoms which is characterized by the planar arrangement of all the atoms and by angles of 120°. Evidently, the distortions of the geometry of the second valence state of carbon in systems with a π-bond at the bridgehead are energetically impossible. In particular, it is for this reason that ketones, such as camphenilone V are completely incapable of enolization



V

which could result in the formation of a double bond at the bridgehead.

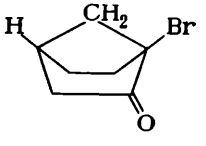
3. *Optical isomerism.* Ketones and other similar compounds, such as norcamphor VI and camphor VII



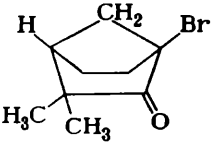
VI VII

each having two asymmetric carbon atoms in the molecule exist nevertheless in only two enantiomeric forms each and do not form diastereomers. This is simply because the bridge can be closed only in the *cis*-position at the two asymmetric carbon atoms at the bridgehead, whereas the change to the antipode configuration of one of the carbon atoms would require the closure of the bridge in the *trans*-position, which is geometrically impossible.

4. *Dynamic stereochemistry.* Since the S_N2 reactions proceed with a Walden inversion, substitutions of this type are impossible at the bridgehead. For example, in bromonorcamphor VIII or in bromocamphenilone IX



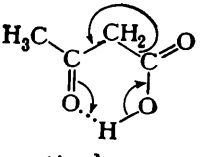
VIII



IX

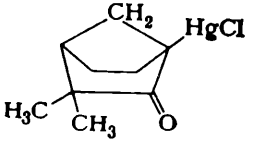
the bromine is immobile, i.e., is not liable to nucleophilic substitution, though normally the bromine in the α-position in ketones is quite mobile. This does not refer to free-radical reactions—the hydrogen at the bridgehead in norcamphor VI can be replaced by bromine under the action of bromosuccinimide. Radical reactions proceed without Walden inversion.

If there is a carboxyl group instead of bromine in bromocamphenilone IX, then such a camphenilonic acid will not lose its carboxyl even on distillation at 312°C in spite of its being a β-ketonic acid. This is also explainable from the viewpoint of Bredt's rule since the decarboxylation of β-ketonic acids proceeds via the cyclic transition state with the formation of the enol of a ketone



which is impossible in this particular case.

There is, however, still another fact which confirms the strength of the bond with the carbon atom at the bridgehead, which cannot probably be accounted for from the standpoint of Bredt's rule. This is the stability of the mercury derivative of camphenilone (A. N. Nesmeyanov, I. I. Kritskaya)



which has absolutely no precedent for α-mercury derivatives of ketones (see Volume IV, "Organoelement Compounds").

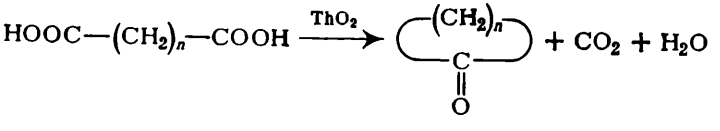
In our opinion, this phenomenon is caused by the absence of the σ,π-conjugation of the neighbouring C—Hg and C=O bonds because of the overlap of the orbitals of the corresponding σ- and π-bonds being spatially impossible (the directions of their axes are mutually perpendicular). Phenomena of this kind for the cases of π,π-conjugation and *p*,π-conjugation will be encountered in studying compounds of the aromatic series; the inactivity of the hydrogen in triptycene and of the bromine in bromotriptycene is also worth mentioning (see Volume III).

6.5. Medium and Large Rings

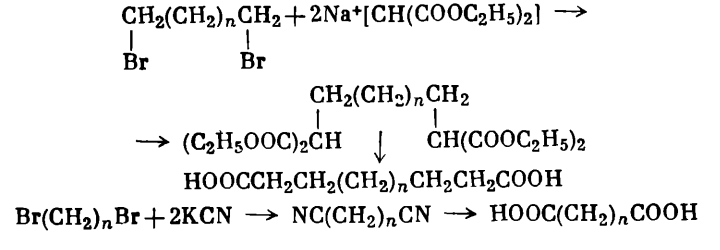
Medium rings are those containing 8 to 12 (more seldom 8 to 14) carbon atoms. Rings containing more than 14 members are called large rings or macrocycles.

A. Methods of Synthesis

Medium-sized and large rings can be built by the same methods used for synthesis of five- and six-membered rings, namely, the pyrolysis of dibasic acids over ThO_2, the condensation of the nitriles and, especially, the acyloin condensation. Many macrocyclic compounds were first synthesized by Ruzicka by the calcination of thorium salts of dibasic acids in vacuum. He succeeded in preparing, through the use of this method, almost all ketones from 5- up to 20-membered and also 34-membered and some other ketones.



Dibasic acids with a normal chain were synthesized by Ruzicka by means of the following two methods:



The esters of the resulting dicarboxylic acids were reduced by sodium in alcohol to glycols, which were then converted into the bromides, and the latter were used for further extension of the chain:

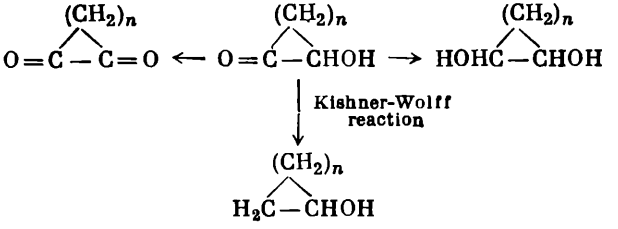
$$ROOC(CH_2)_nCOOR \longrightarrow HOCH_2(CH_2)_nCH_2OH \longrightarrow BrCH_2(CH_2)_nCH_2Br$$

Compounds with medium rings can be obtained by the Dieckmann condensation (ester condensation) and by the condensation of dicarboxylic nitriles (Thorpe) (see page 230). All these methods afford good yields of five-, six- and seven-membered rings, but the yield falls off sharply (sometimes down to 0 per cent) in the case of medium-sized rings, particularly 9- and 10-membered rings. With lengthening of the chain to 13 carbon atoms upwards the yield of large rings increases somewhat, but not too much.

The low yield of macrocyclic compounds is attributed to the low probability of encounter of terminal groups (the entropy factor). As the chain length increases, the probability that the ends of two different molecules will come together becomes greater than the probability of collision between the ends of a single molecule. To reduce the possibility of occurrence of side reactions, K. Ziegler proposed the **method of extreme dilution.** Generally speaking, the condensation may proceed either intramolecularly, with the formation of cyclic products, or intermolecularly, with the formation of dimers and polymers. The rate of cyclization is proportional to the first-power concentration of the substance, whereas the rate of linear condensation is proportional to the square of the concentration since the reaction is bimolecular. Therefore the dilution reduces the possibility of intermolecular condensation. The method of extreme dilution consists in the following: first, large amounts of solvent are used and, second, the reactant substance is added dropwise to the solution containing a condensing agent. The extreme dilution method gave good results in the preparation of large-ring compounds, but medium-sized rings, particularly 9- to 11-membered rings, were obtained in yields of 0.2-2 per cent. The **acyloin method** (Stoll, Prelog) in which ring formation takes place on the surface of sodium, made it possible to sharply increase the yield of medium rings. When an ester of a dicarboxylic acid is gradually added to a boiling solvent (xylene, toluene) containing molten sodium, the **acyloin condensation** (cyclization) occurs:

$$C_2H_5OOC(CH_2)_nCOOC_2H_5 \xrightarrow{Na} O{=}\underset{\text{Acyloin}}{\overset{(CH_2)_n}{\diagup\diagdown}}C{-}CHOH$$

The resulting hydroxyketone (acyloin) can then be subjected to further conversions: into a diketone, a glycol, a hydrocarbon, etc.



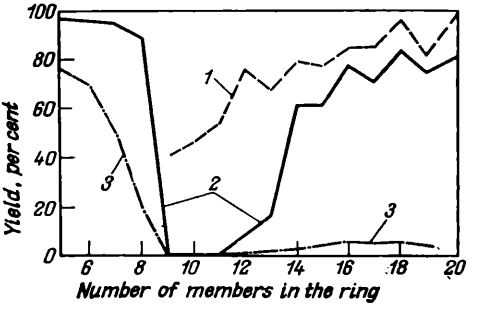


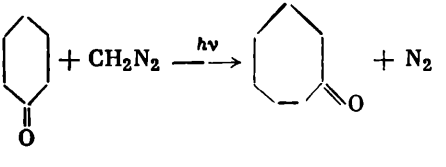
Fig. 6.2.

Yields of derivatives of cycloalkanes in various methods of cyclization: 1— acyloin condensation (Prelog); 2— Thorpe-Ziegler method (condensation of nitriles of dicarboxylic acids under conditions of extreme dilution); 3— dry distillation of rare-earth salts of dicarboxylic acids (Ruzicka).

Figure 6.2 gives the yields of alicyclic compounds prepared by different methods.

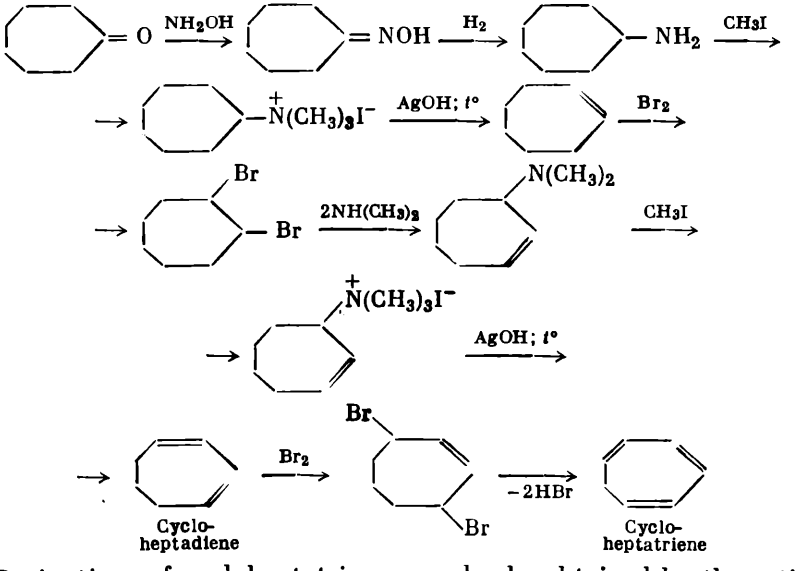
B. Derivatives of Cycloheptane

Compounds of the cycloheptane series are synthesized by one of the general methods of cyclization or by extension of six-membered rings to seven-membered ones. For instance, suberone (*cycloheptanone*) can be prepared by various methods from derivatives of suberic acid (page 269) or by the action of diazomethane on cyclohexanone in light:

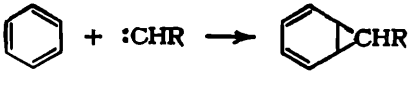


Cycloheptanone can be utilized for preparation of other derivatives of compounds of the cycloheptane series (see above for cyclopentanone).

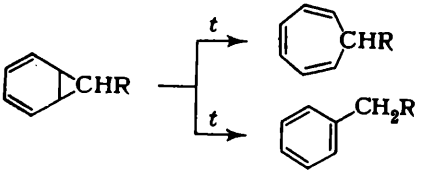
Extremely interesting are derivatives of a maximally unsaturated hydrocarbon—**cycloheptatriene** (*tropilidene*). Their synthesis was first accomplished by Willstätter, who used cycloheptanone as a starting material, according to the following scheme:



Derivatives of cycloheptatriene can also be obtained by the action of fatty diazo compounds on benzene. The carbene formed initially in the decomposition of a diazo compound adds on to benzene, and the conversion into derivatives of norcarane takes place:

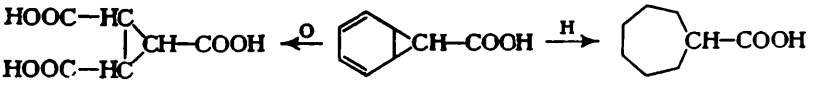


The bicyclic compound formed on pyrolysis undergoes isomerization:

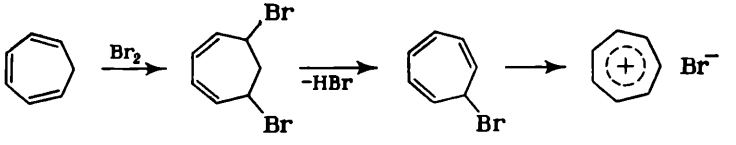


The structure of the product of the interaction between benzene and diazoacetic ester is proved by the fact that on oxidation it gives

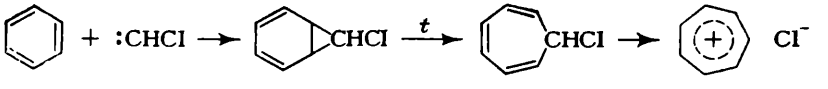
cyclopropane-1,2,3-tricarboxylic acid and on reduction, cycloheptanecarboxylic acid:



Cycloheptatriene itself is a reactive unsaturated, readily polymerizable compound soluble in organic solvents and insoluble in water. The tropylium bromide obtained from cycloheptatriene is a salt, in which the cation is an aromatic ion—**tropylium ion** (for more detail, see Volume IV, "Carbanions"):



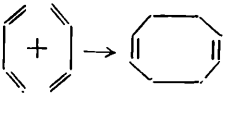
Tropylium bromide is a salt-like compound, dissolves well in water, and when silver nitrate is added the bromide ion is completely and immediately precipitated as AgBr. Using the method worked out by D. N. Kursanov and M. E. Volpin, it is possible to prepare tropylium salts as a result of addition to benzene of the chlorocarbene generated from methylene chloride:



C. Derivatives of Cyclooctane

The derivatives of cyclooctane can be prepared by the methods described on page 261, and cyclooctapolyenes are obtained by the Reppe condensation of acetylene and by the Ziegler condensation of butadiene.

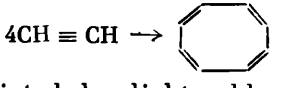
Butadiene dimerizes over Ziegler catalysts [$Al(C_2H_5)_3 + TiCl_3$] to **cyclooctadiene**:



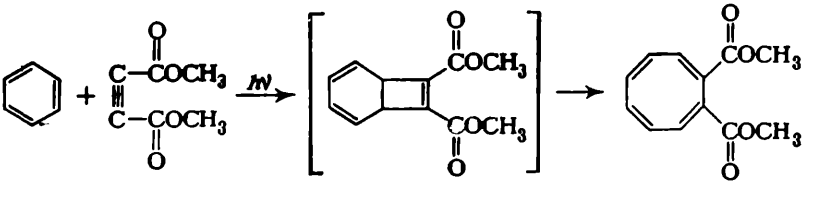
This diene forms a π-complex with "zero-valent" nickel:

The complex decomposes on heating to a metal and the parent unsaturated hydrocarbon (Wilke).

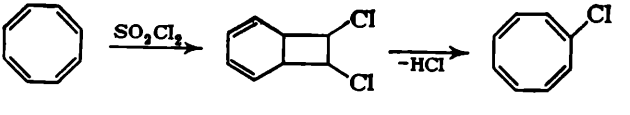
Of particular interest is **cyclooctatetraene**, an eight-membered ring with four conjugated double bonds. The cyclooctatetraene molecule has a non-planar arrangement of atoms (the "tub" structure) and is not aromatic. Cyclooctatetraene was first prepared by Willstätter who used a multi-stage synthesis analogous to the synthesis of cycloheptatriene described above. The starting material for the synthesis of cyclooctatetraene was the alkaloid pseudopelletierine (see Volume IV, "Alkaloids"). At present, cyclooctatetraene is prepared by the Reppe method—the condensation of acetylene on heating under pressure in the presence of nickel cyanide (in the form of an ammine complex):



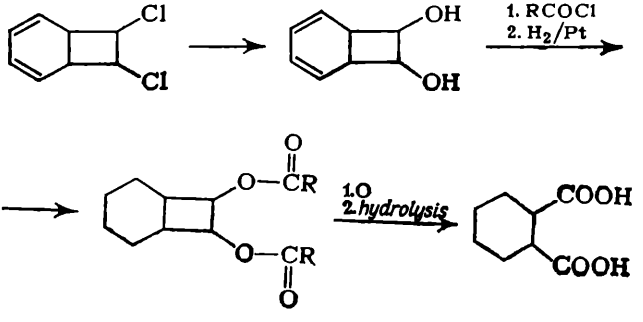
Benzene when irradiated by light adds certain derivatives of acetylene to form derivatives of cyclooctatetraene:



Cyclooctatetraene is easily hydrogenated over Pt or Ni to cyclooctane. Under other conditions it can be reduced to cyclooctene or to cyclooctatriene. Many of the reactions of cyclooctatetraene are accompanied by the isomerization of the skeleton. For example, the chlorination by sulphuryl chloride gives the dichloro derivative of bicyclo[4.2.0]octa-2,4-diene, which when subjected to dehydrohalogenation with $NaN(C_2H_5)_2$ yields chlorocyclooctatetraene:

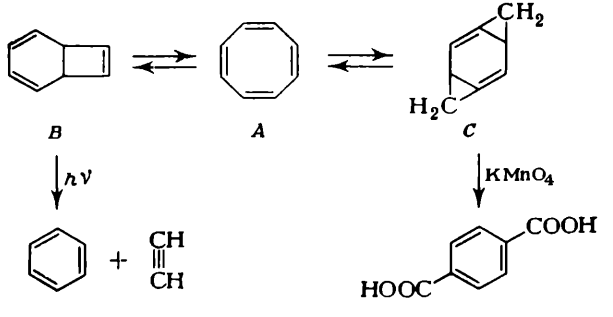


The structure of the bicyclic compound thus obtained is proved, in particular, by its conversion into hexahydrophthalic acid according to the scheme:



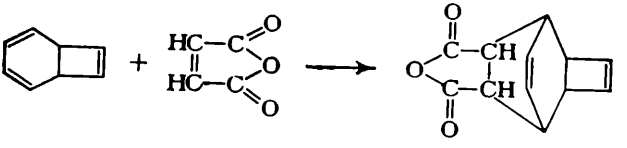
The oxidation of cyclooctatetraene leads directly to benzene-1,4-dicarboxylic acid—terephthalic acid.

Tanaki and Akida converted cyclooctatetraene into benzene and acetylene by subjecting it to ultraviolet radiation. In these reactions, cyclooctatetraene reacts as a tautomeric compound:



A number of other reactions are known, in which cyclooctatetraene reacts in any one of its three forms, *A*, *B*, and *C*. The results of the hydrogenation reaction described above correspond to structure *A*; the decomposition into benzene and acetylene, to structure *B*; and the oxidation to benzene-1,4-dicarboxylic acid, to structure *C*. We may add also the oxidation of cyclooctatetraene by NaOCl, which yields *p*-benzodialdehyde. The chlorination with SO_2Cl_2 involves structure B. Numerous reactions of diene synthesis based on various dienophiles (maleic anhydride, tetracyanoethylene, etc.) also

proceed as expected of the *B* form. For example,

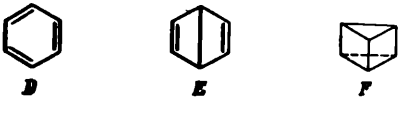


It is evident that the form *A* does not enter into diene synthesis because it is non-planar and therefore has no conjugated π-bonds (at least it is devoid of complete conjugation). On the contrary, the form *B*, like 1,3-cyclohexadiene, has conjugated π-bonds.

XXIII. Valence Isomerism and Tautomerism

A question, however, arises: Do the forms *B* and *C* actually exist or are they only "reaction forms", i.e. structures formed in the course of the reaction under the action of a reagent? In other words, do we deal here with a case of **tautomerism** with the independent existence of individual isomeric compounds *A*, *B*, and *C* capable of interconversion according to the laws of tautomeric equilibrium? It should be stressed that such **valence tautomerism** is associated with the redistribution of valence bonds*, i.e., electrons, and not atoms (hence its second, highly inaccurate, name *electronic tautomerism*), and thus refers neither to cationotropy (see page 83) nor to anionotropy.

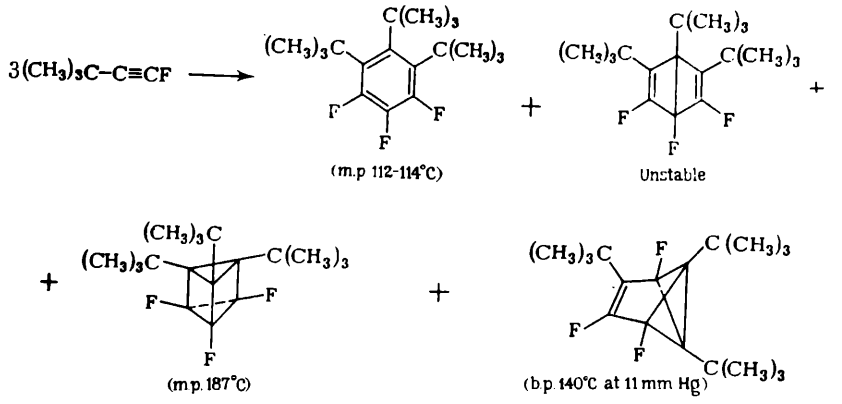
It should also be noted that valence isomerism (without reversible interconversion of such isomers) is known at present for a number of cases. The valence isomers of benzene serve as an example:



When heated the isomers *E* and *F* are irreversibly converted into benzene *D*.

* The alteration of the bond system results from the change of the bond length and valence angles, i.e., is a consequence of the change of the geometry of the molecule.

The spontaneous polymerization of *tert*-butylfluoroacetylene gives four valence isomers depicted below:



These isomers have been separated from one another chromatographically and their structures have been elucidated by means of NMR spectra and optical spectra (Wiche et al.).

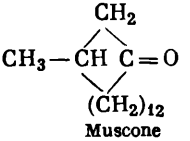
The hexamethyl derivative of Ladenburg benzene* was prepared in 1966 by Schaeffer by a preparatively suitable reaction: the benzene solution of dimethylacetylene with aluminium chloride was allowed to stand. The resulting compound—**hexamethylprismane**—undergoes isomerization at room temperature (more rapidly on heating) to its valence isomer—hexamethylbenzene. In these cases, just as in the case of true isomerism, there is an energy barrier between the individual substances and an activation energy is required for their interconversion.

The presence of the tautomeric forms *A* and *B* for cyclooctatetraenes was confirmed unambiguously by R. Huisgen. Studying the kinetics of diene synthesis of cyclooctatetraene with dienophiles, Huisgen showed that the form *A* does not enter into reaction and that the reaction rate with excess of dienophile is independent of the concentration of the latter and is governed by the rate of conversion of *A* into *B*. Huisgen succeeded in determining the concentration of tautomer *B* in dioxan solution at 100°C and established that it is very low—only 0.01 per cent. From observations of the rate of diene synthesis at various temperatures (in ethylacetate solution) he determined the activation energy parameters of the tautomerization process [$\Delta H^* = 25.0$ kcal/mole and $\Delta S^* = 3$ cal/(deg·mole)], the values of which were found not to exceed those of typical thermodynamic constants for ordinary reactions.

* Since in the last century Ladenburg suggested the prismatic formula for benzene, this structure (formula *F*) is called the *Ladenburg benzene*. The modern name for derivatives of the Ladenburg structure is *prismanes*.

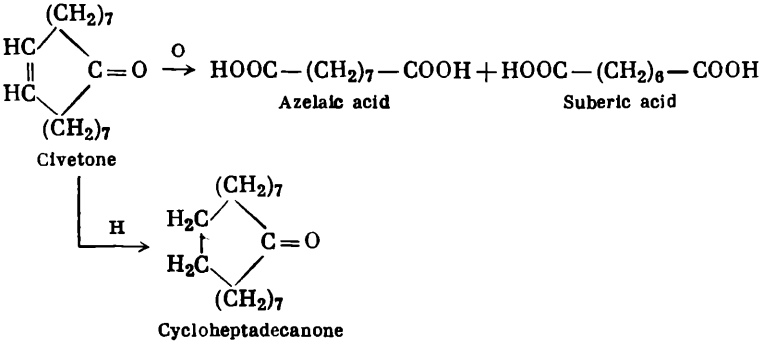
D. Derivatives of Other Cycloalkanes

Higher alicyclic compounds have been studied relatively little. The greatest importance is attached to more available cyclic ketones. All the higher ketones, beginning with cyclododecanone, have a characteristic smell. Ketones with 10, 11, and 12 carbon atoms in the ring smell of camphor and those with 14 to 18 atoms have the smell of musk. Cyclopentadecanone is used in perfumery under the name of **exalton**. The flavouring matter of animal musk is chiefly the ketone **muscone**



Muscone

Civetone, the flavouring matter of civet, is an unsaturated ketone with 17 carbon atoms in the ring. The oxidation of civetone gives azelaic and suberic acids, and the hydrogenation of its double bond yields cycloheptadecanone:



Civetone

Azelaic acid

Suberic acid

Cycloheptadecanone

Cycloheptadecanone is oxidized to tetradecanedicarboxylic acid.

XXIV. The Transannular Effect

The difficulty of formation of medium-sized (8- to 13-membered) rings and their somewhat higher heats of combustion (per methylene group) are mainly associated with a new type of non-classical strain in the ring. It is caused by the fact that certain hydrogen atoms situated on opposite sides of the ring come too close together and are

mutually repelled. This type of interaction called **transannular interaction** produces **transannular strain.** This effect is especially pronounced in 9- to 11-membered rings.

Judging by the X-ray data, we may conclude that the cyclodecane molecule in the solid state has the conformation depicted in Fig. 6.3. From this figure (the end-on view of the molecule) it is clearly seen that the three hydrogen atoms above the plane of the ring and those below the ring plane are especially close to one another. This interaction leads to a certain departure of the bond angles from the tetrahedral angle and to a number of anomalous reactions.

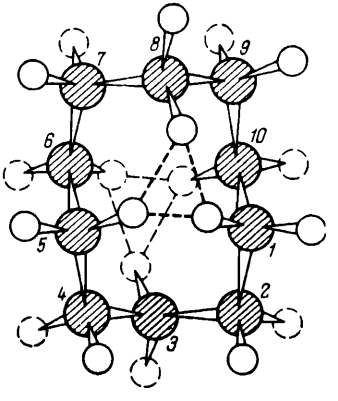
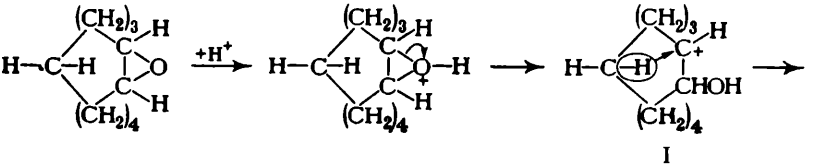


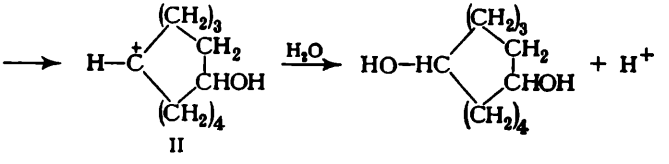
Fig. 6.3.
Cyclodecane.

The greater number of known transannular reactions occur in such a way that the positive carbonium centre which arises as a result of a reaction on one of the ring carbon atoms migrates to another carbon atom, which, though being remote along the chain, is close in space. This transfer of the reaction centre takes place by the hydride-shift mechanism, i.e., the migration of a hydrogen atom with a pair of bonding electrons. We shall cite some examples of the reactions of this type discovered independently by Cope and Prelog in 1952.

It might seem that the acid hydrolysis of cyclodecene α-oxide must lead to 1,2-cyclodecanediol (cyclodecane-1,2-diol). But in reality this glycol is not formed at all. Instead, a mixture of products is obtained, in which 1,6-cyclodecanediol predominates. Similarly, cyclononene oxide yields 1,5-cyclononanediol, and cyclooctene oxide, a mixture of the normal reaction product and the 1,4-diol. The mechanism of the reaction is as follows. When the α-oxide ring of cyclodecene oxide is opened by the action of a proton, carbonium ion I is formed. Then the hydrogen atom in the form of a hydride ion jumps to the spatially nearest positively charged carbon atom and carbonium ion II is formed, which adds on a hydroxyl group:



I



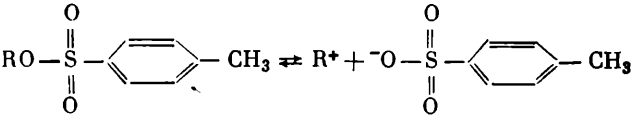
II

This is only an approximate mechanism of the conversion. It is possible that the hydride-ion transfer begins simultaneously with the opening of the oxide ring, in which case the absence of the 1,2-diol in the reaction products becomes understandable.

Thus, the hydroxyl groups are found to be in the 1,6-positions and not in the neighbouring positions as should be expected on the basis of classical conceptions.

The conversion of α-oxides into glycols is a convenient reaction for the investigation of the transannular effect because different isomeric glycols result from normal and transannular reactions.*

The transannular migration of a hydride ion has also been observed in other cases, where the occurrence of such migrations has been proved by means of tracer atoms. Let us consider, for example, the hydrolysis of *p*-toluenesulphonates (tosylates)** of cyclodecanol. The hydrolysis proceeding by the S_N1 unimolecular mechanism consists of the reversible formation of a carbonium ion:



where R^+ is the cyclodecyl carbonium ion $C_{10}H_{19}^+$, which can then react in several ways: it combines immediately with a hydroxyl or is converted into an unsaturated compound (proton expulsion), or else is converted, as a result of a hydride shift, into another cation which

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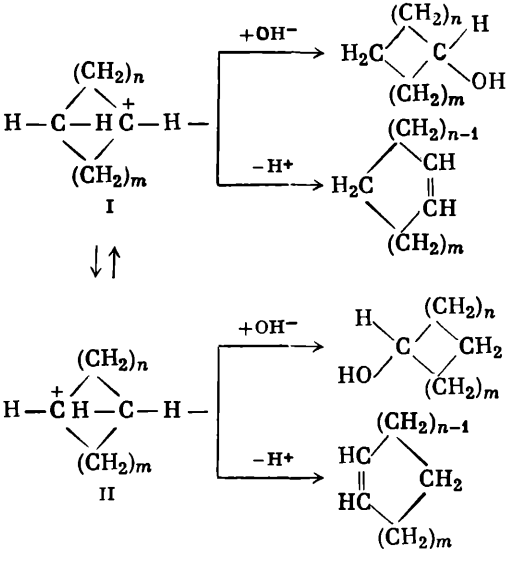
* In actual fact, the reaction is considerably more complicated than the one represented by our scheme. For example, the reaction of cyclodecene with performic acid (which proceeds through the stage of formation of an α-oxide) gives eight products more, apart from the glycol. It turned out to be enormously difficult to separate these compounds, to identify them and to prove their structure.

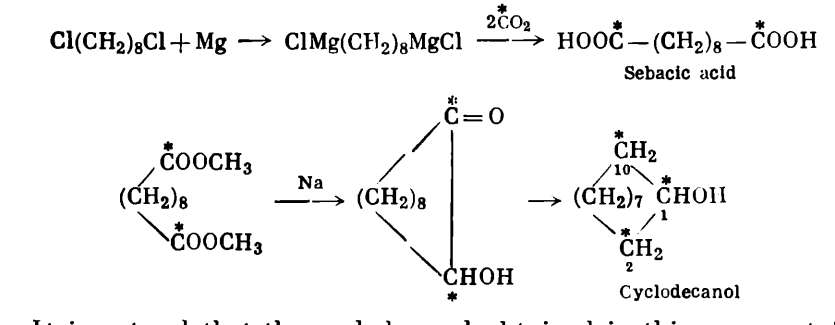
** **Tosyl** is the residue of *p*-toluenesulphonic acid, $-CH_3C_6H_4-S(=O)_2-$; **tosylate** is the ester of this acid.

is also capable of giving an alcohol or unsaturated compound:



The products formed from both cations (I and II) are identical. But if one or more carbon atoms in the molecule are labelled with ^{14}C, the products of normal and transannular reactions will contain the tagged carbon atom in different positions relative to the double bond (in cyclodecene) or to the hydroxyl (in carbinol).

Using the acyloin condensation, Prelog and his coworkers accomplished the synthesis of ^{14}C-labelled cyclodecanol from sebacic acid labelled across the carboxyl group:

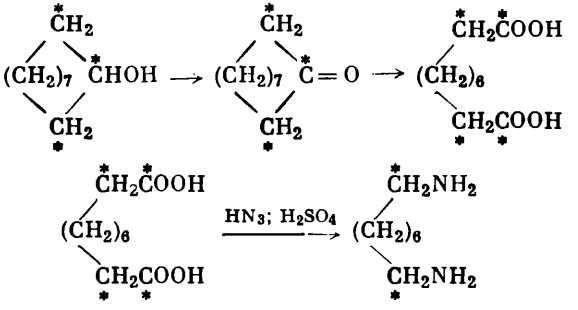


Sebacic acid

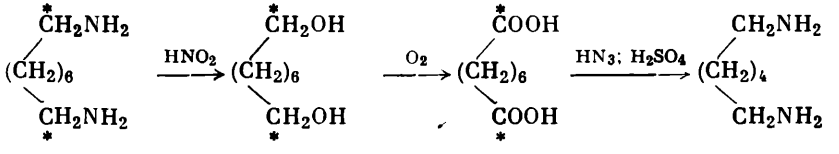
Cyclodecanol

It is natural that the cyclodecanol obtained in this way contains 50 per cent of radioactivity in position 1 and 50 per cent in the α-positions 2 and 10 (of course, in actual fact all the 50 per cent of radioactivity is contained in one of the α-carbon atoms but since they are all equivalent, it may be stated that each atom is 25 per cent

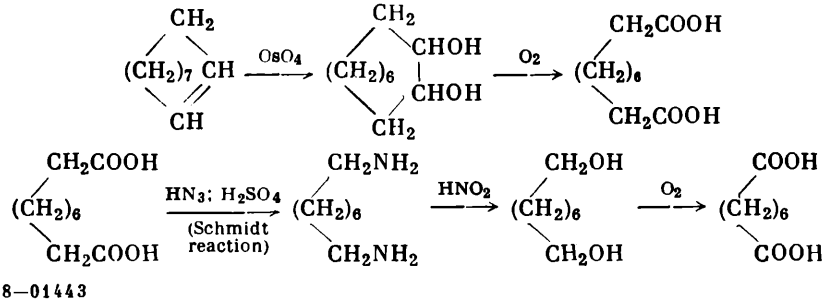
radioactive). To prove this distribution of activity in the resulting alcohol, it is oxidized to sebacic acid. In this acid, the carboxyl groups must be 75 per cent and the α-carbon atoms 25 per cent radioactive. This is confirmed by the fact that octamethylenediamine obtained from sebacic acid by the Curtius-Schmidt method contains 25 per cent of radioactivity

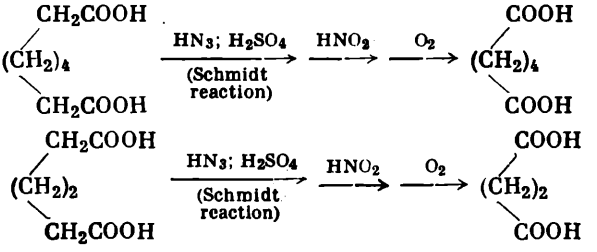


and hexamethylenediamine prepared from octamethylenediamine (the conversion into a glycol by the action of HNO_2, the oxidation of the glycol to suberic acid and the rearrangement of the latter by the Curtius-Schmidt method), is practically inactive:



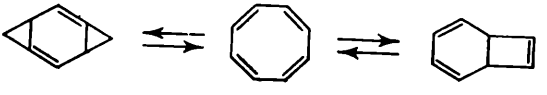
Let us now consider the products of hydrolysis of cyclodecanol tosylates labelled with ^{14}C in positions 1, 2 and 10. The hydrolysis occurring by the unimolecular mechanism results in the predominant formation of cyclodecene with a small amount of cyclodecanol. A proof of radioactivity distribution is provided by the oxidation of these compounds to sebacic acid and by the gradual "cutting-off" of the ends of the chains:





It has been found that even succinic acid obtained from sebacic acid contains a considerable fraction of the radioactive isotope ^{14}C. Not only the carbon that has carried the tosylate substituent is tagged but also the carbon atom situated on the other side of the ring. Hence, in this case too there is observed a transannular hydride transfer.

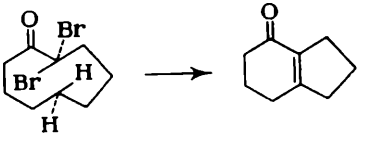
Transannular reactions of another type, not associated with hydride transfer, have been detected in certain cyclic polyenes. For example, cyclocctatetraene, as mentioned on page 266, is capable of transannular cyclization leading to valence tautomerism:



This type of transannular cyclization is also characteristic of cyclononatriene:

Such tautomeric transformations involve no considerable change in the geometry of the molecule (i.e., its form).

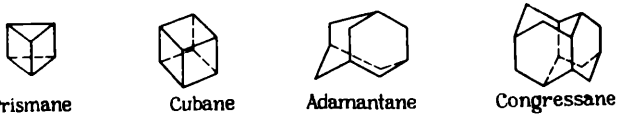
Transannular cyclization also occurs when 2,2-dibromocyclononanone (or 2,2-dibromocyclodecanone) is treated with organic bases:



Transannular reactions are also encountered in the heterocyclic series.

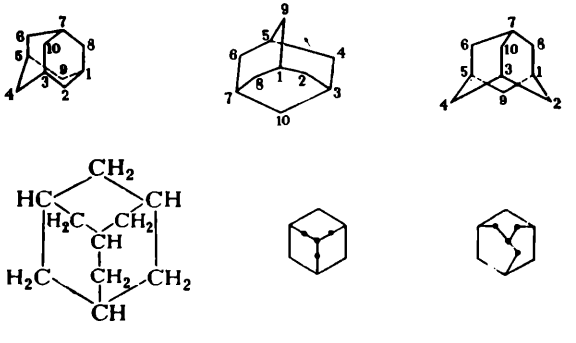
6.6. Polycyclic Compounds

Alicyclic compounds with a higher degree of condensation are also known, which are composed of four or five fused rings; for example,



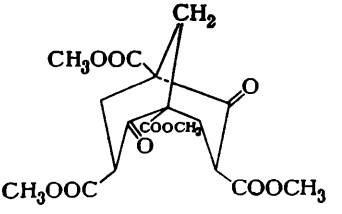
Of these, **adamantane** has long been known. It was isolated from petroleum by S. Landa and V. Machacek in 1933 (its content in petroleum is about 0.0004 per cent). Special interest to adamantane is accounted for by the fact that it is the structural unit of diamond. The crystal of diamond is, as it were, a polymer built up of the adamantane skeleton in which all the C—H bonds have been replaced by C—C bonds.

The molecule of adamantane has a high degree of symmetry; all the three cyclohexane rings are fixed in the chair form and are free from angle strain. The following are the various representations of the formula of adamantane (tricyclo[3.3.1]decane):



The melting point of adamantane (269°C) is unusually high for hydrocarbons; adamantane sublimes readily, is distilled with steam and crystallizes well. These properties have made it possible to isolate adamantane from a mixture of the various hydrocarbons contained in the corresponding petroleum fraction.

Adamantane has now been synthesized in various ways. The starting material was in most cases the so-called **Meerwein ester**

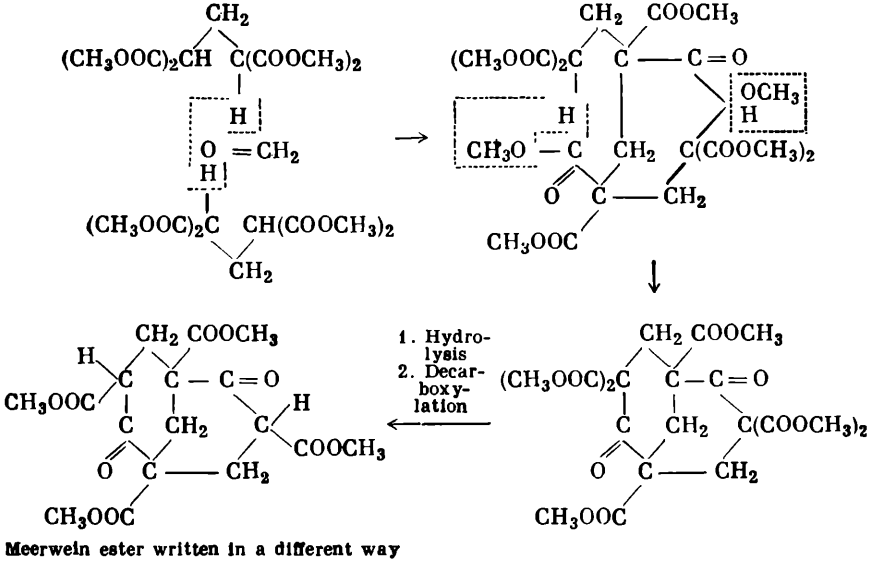


resulting from the condensation of formaldehyde with malonic ester.

The formation of the Meerwein ester in this condensation reaction may be formulated as follows:

$$(CH_3OOC)_2CH_2 + CH_2O + CH_2(COOCH_3)_2 \xrightarrow[-H_2O]{}$$

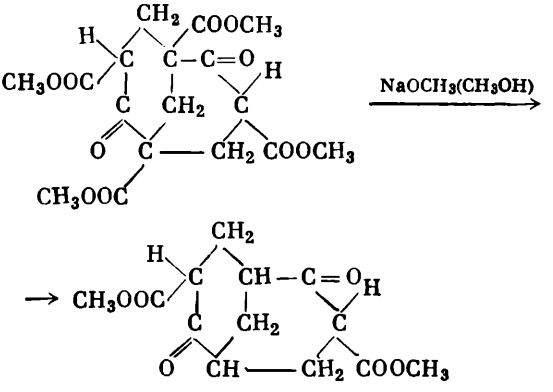
$$\longrightarrow (CH_3OOC)_2CH-CH_2-CH(COOCH_3)_2$$



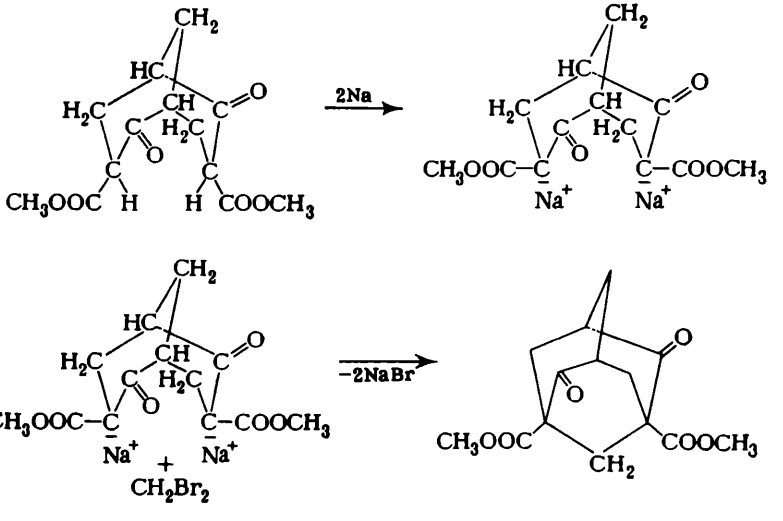
Meerwein ester written in a different way

The carboxyl groups at the tertiary angular atoms of Meerwein ester in the β-position relative to the ketonic carbonyl groups were removed by decarboxylation in alcohol in the presence of sodium

methoxide:

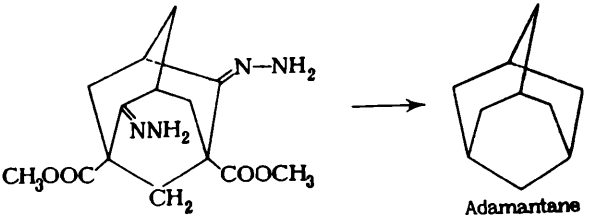


In the resulting keto ester, the hydrogen atoms at the carbon atoms situated between the ester and keto groups are mobile, just as in acetoacetic ester, and can be replaced by sodium. In the condensation of the sodium derivative with methylene bromide, ring closure occurs and the adamantane structure is formed (for clarity, the formulas are given with C^- and Na^+ bonds and not with enolate linkages):

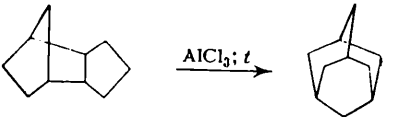


In the compound obtained, the keto groups are reduced by the Kishner-Wolff reaction (via hydrazones) and the ester groupings are

saponified and then decarboxylated:



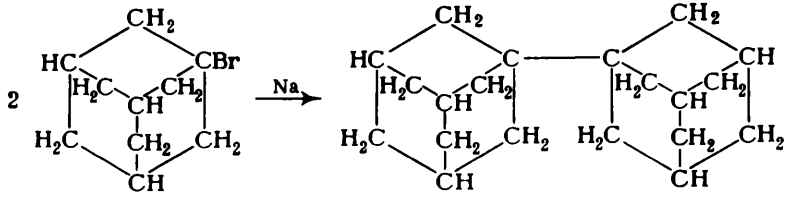
Adamantane can also be prepared by the isomerization of other polycyclic hydrocarbons in the presence of aluminium chloride; for example,



The structure of adamantane has been proved (apart from synthesis reactions) by measuring the parameters of the molecule by electron diffraction and X-ray methods. The adamantane molecule is free from angle strain. Its structure is ruptured with great difficulty.

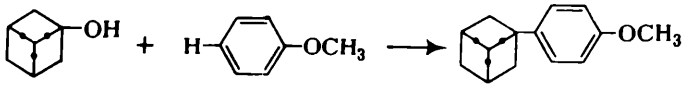
When adamantane is boiled with bromine, a monosubstituted product results (bromine replaces hydrogen on one of the tertiary carbon atoms). This bromination reaction is an ionic process since it is speeded up in the presence of Lewis acids, such as aluminium chloride, and its rate is unaffected by peroxides. Four bromine atoms can be incorporated into the molecule in the presence of Lewis acids.

The action of sodium on bromoadamantane in xylene gives **diadamantane:**



tert-Bromoadamantane is relatively easily hydrolysed and is not much inferior in this respect to *tert*-butyl bromide. In the corresponding hydroxy- and methoxyadamantanes the groups OH and OCH_3 are replaced by chlorine even by the action of cold hydrochloric acid (Stetter, F. N. Stepanov). Other reactions of elimination of a hydroxyl group also proceed easily; an example is the condensation of hydroxyadamantane with anisole, which takes place in the absence

of a catalyst:

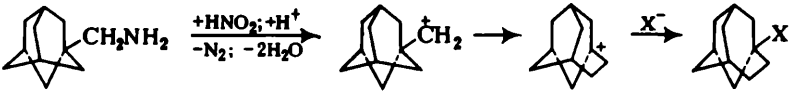


These reactions provide a proof of the stability and the ease of formation of the **adamantonium ion**, for example, in a bromination reaction:

The adamantonium ion is energetically more favourable than, say, the norcamphane carbonium ion which bears a positive charge on the bridge carbon atom. This is accounted for by the fact that the camphane molecule is considerably strained and the change of the bond angles upon conversion to the cation, which is accompanied by the forcing-in of the bridge atom into the molecule (since the cation tends to assume a flat configuration), increases the strain in the cation

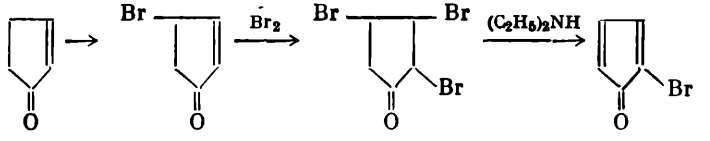
very sharply and even more considerably. But the adamantane molecule is free from angle strain. The resulting cation adopts a form intermediate between the initial form of the molecule and the form in which the positively charged carbon atom is in the same plane with the three adjacent carbon atoms.

The adamantylmethyl ion, which can be prepared by the action of acid on adamantylcarbinol or by the action of nitrous acid on the corresponding amine, undergoes the skeleton rearrangement to the homoadamantyl ion which contains one additional CH_2 unit and is stabilized by the capture of the anion from the medium (F. N. Stepanov):

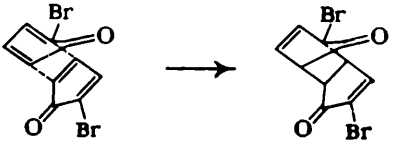


The derivatives of **cubane** have been synthesized in recent years. As an example, let us consider the synthesis of cubanedicarboxylic acid. The action of bromosuccinimide on 2-cyclopentenone affords a bromine derivative which adds bromine across the double bond. The

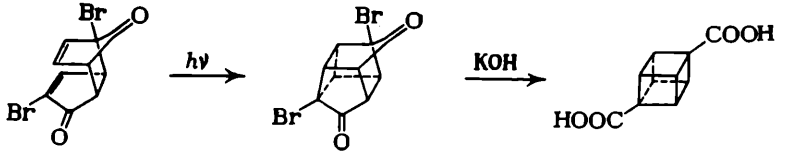
resulting 2,3,4-tribromo-1-cyclopentanone readily eliminates two molecules of hydrogen bromide under the influence of the amine to form α-bromocyclopentadienone:



which dimerizes spontaneously:

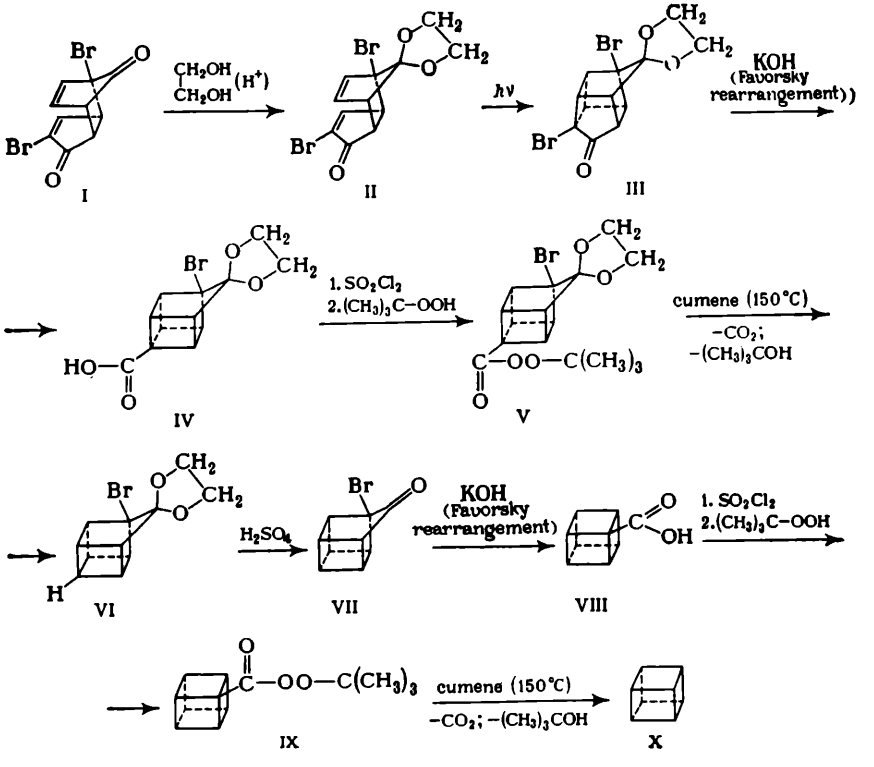


The resulting dimer has two double bonds. Under the influence of radiation it undergoes cyclization at the expense of these double bonds, a new four-membered ring being formed. The resulting compound, which contains four five-membered and two four-membered rings, undergoes a Favorsky rearrangement under the action of 50-percent alkali. This reaction yields cubanedicarboxylic acid:



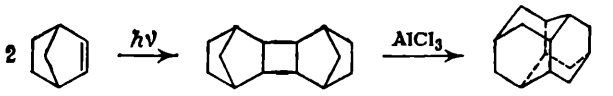
In 1966 Eaton and Cole synthesized cubane itself by similar methods, starting with the same dimer of bromocyclopentadienone I, which was converted by the action of ethylene glycol in acid medium into cyclic ketal II which undergoes cyclization by the action of light into compound III. When the resulting compound is treated with alkali, a Favorsky rearrangement takes place, followed by the conversion of the acid IV obtained into the acid chloride which is reacted with *tert*-butyl hydroperoxide to give a peroxide of the ester type V. When heated in isopropylbenzene (cumene) up to about 150°C the peroxide V decomposes by a free-radical mechanism and captures a hydrogen atom from isopropylbenzene, this hydrogen atom taking the place of the carboxyl leaving in the form of CO_2. This is followed by the hydrolysis of ketal VI and the reversion to the ketonic function VII. A new Favorsky rearrangement is accomplished by the action of alkali and the resulting acid VIII is again (via the acid chloride) esterified by *tert*-butyl peroxide to peroxide IX, which,

like the previous one, undergoes a free-radical decomposition to isopropylbenzene at 150°C, forming cubane X:



Cubane is a crystalline compound with m.p. 130-131°C, which sublimes; it was recrystallized from methanol. A proof of its structure has been obtained by means of physical methods. The mass spectrum has a peak at *m/e* of 104, and the proton magnetic resonance spectrum has only one peak (all the hydrogens being equivalent); the infrared spectrum in the region of 4000 to 660 cm^{-1} has three lines only: 3000, 1231 and 851 cm^{-1}, which proves the absence of multiple carbon-carbon bonds.

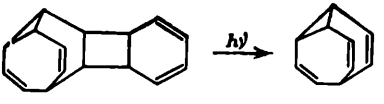
The symbol of the XVII International Congress on Pure and Applied Chemistry was the formula of the then unknown symmetric alicyclic compound built up of five cyclohexane rings. This hydrocarbon was synthesized in 1965 by the isomerization of the dimer of norbornene and was given the name congressane (pentacyclo-[7.3.1.$1^{4,12}$.$0^{2,7}$.$0^{6,11}$]tetradecane):



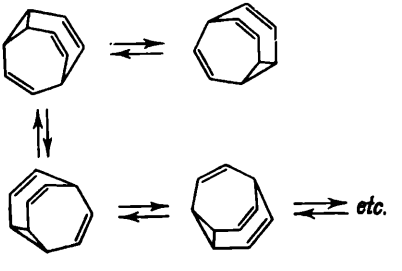
(m.p. 262 °C)

Its structure has been proved by measuring the parameters of the molecule in X-rays and confirmed by other physical methods.

One of the most interesting polycyclic hydrocarbons is the so-called **bulvalene**, or tricyclo[3.3.2.0]deca-2,7,9-triene, obtained in 1965 by Schreider by the ultraviolet irradiation of the hydrocarbon given below—the dimer of cyclooctatetraene. In this photochemical reaction, benzene is split off from the dimer:



This hydrocarbon is noted for its ability to undergo the Cope rearrangement continuously at a temperature above 100°C. The Cope rearrangement (see Volume IV) can be depicted in this particular case by the following formulas:



At an elevated temperature (100°C) this hydrocarbon, as a result of such repeated rapid rearrangements, shows the equivalency of protons according to the NMR spectrum, which has one well-defined peak at $\tau = 5.8$. This means that all the hydrogen atoms are equivalent. But at —25°C no such rearrangement takes place and the hydrogens are no longer equivalent and the NMR spectrum becomes complicated.

XXV. Physical Methods of Elucidation of the Structure of Organic Molecules II*

(A) Structure Determination by Fragmentation Mass-Spectrometry

If the molecule of an organic compound, which is in the gaseous state under conditions of high vacuum (10^{-7} to 10^{-9} mm Hg), is subjected to the bombardment with a beam of medium-energy electrons (25-70 electron-volt), one of the valence electrons is removed and a highly excited, positively charged ion called the **molecular ion** (M^+) is formed. As a rule, electron bombardment knocks out one of the electrons of the free (unshared) electron pair of a heteroatom or one of the π-electrons of an aromatic system or a multiple bond. The molecular ion being quite labile due to the high degree of excitation, undergoes a number of successive breakdowns with the formation of positively charged ions (fragments) and neutral molecules or radicals.

The ions after being accelerated out of the ion source by an electrostatic field enter a perpendicularly directed magnetic field in which they change their initial direction differently according to their mass-to-charge ratio (*m/e*) and are thus separated into *m/e* groups. The ion beam that reaches the collector is amplified and recorded by an oscillograph or a recording device. In the resulting mass-spectrum (a chart of the mass/charge ratio against the intensity or abundance of each ionic species) of the compound under study, each ion forms a characteristic peak, the intensity of which corresponds to the *m/e* of the *ion* formed in the breakdown process.

The breakdown path of the molecular ion and the subsequent fissions of fragment ions are determined by the structure of the organic molecule itself, i.e., by the set and sequence of atoms, groups and bonds in it. The mass-spectrum reflects sufficiently precisely the constitution of the molecule and can be used to elucidate its structure. The breakdown of the molecule, called **fragmentation**, includes both homolytic and heterolytic fissions of the bonds, though the former are more often observed. Thus, in contrast to other physicochemical methods used for the investigation of organic compounds, **mass spectrometry** is based on the destruction of the molecule, more exactly, of the excited positive ion produced from the molecule of an organic compound by the electron impact. In this respect, the mass-spectrometric method is similar to the classical methods of elucidation of the structure of organic compounds through molecular

* Physical methods of investigating the structure of organic molecules are discussed in Volume I.

destruction, but in mass spectrometry the entire course of fragmentation is immediately recorded and less than one milligram of sample is required for the entire complicated fragmentation process.

As a whole, the fragmentation of ions obeys the regularities typical of organic reactions. For example, energetically more favourable tertiary carbonium ions are usually produced by fragmentations in preference to primary or secondary ions (see Volume IV, "Carbonium Ions"), and also stable allyl and benzyl groupings, ions and radicals; dehydration and decarboxylation reactions take place readily, etc.

The decomposition or fragmentation of the molecular ion usually involves the rupture of the bonds near the site of localization of

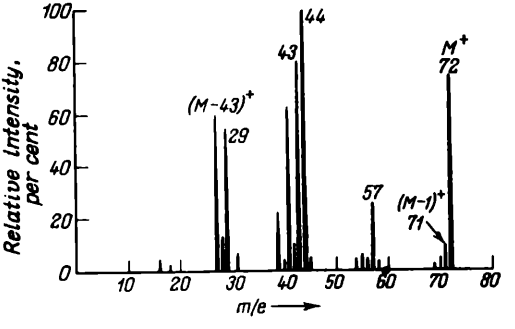


Fig. 6.4.

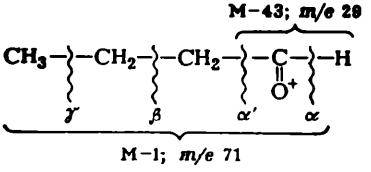
Mass-spectrum of butyraldehyde. Formation of the peak of the $(M - 1)^+$ ion with m/e 71 and of the peak of the M^+ ion with m/e 72.

the positive charge, which allows the modes of fragmentation (or bond fissions) to be classified as follows. The bond fission at the carbon atom linked to a heteroatom (i.e., a non-carbon atom) or to the group on which the positive charge is localized is called the α-fission. The ruptures of the successive C—C bonds are respectively termed the β-, γ-, etc. fissions; α-ruptures are most common. Bond ruptures that occur without migration of individual atoms or groups are known as ordinary fissions, and those which are accompanied by such a migration are called rearrangement fissions.

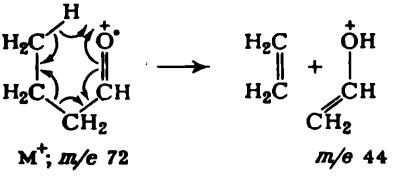
If we examine the mass spectrum, say, of *n*-butyraldehyde (Fig. 6.4), we can detect a number of peaks corresponding to the ions resulting from the various fissions. The formation of the peak of the ion $(M - 1)^*$ with $m/e = 71$ and the peak of the ion $(M - 43)^*$ with $m/e = 29$ is caused by ordinary α-fissions. As a result of one such fission (α), a hydrogen atom is eliminated, and another fission

* $(M - 1)$, $(M - 43)$, etc., denote singly charged ions by 1 and 43 mass numbers lighter than the parent molecule. (M is the molecular weight of the parent molecule.)

(α') eliminates an alkyl in the form of the radical $\cdot C_3H_7$. As seen from a comparison of the intensities of these peaks, the α'-fission with elimination of the heavier radical is preferential:

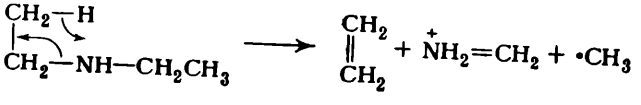


The peaks at $m/e = 57$ and 43 are due, respectively, to β- and γ-fissions. The most intense peak in the spectrum (taken as 100 per cent) at m/e 44 is, however, due to the ion formed as a result of the rearrangement β-fission with migration of a γ-hydrogen atom. The fission occurs in the six-membered transition state:

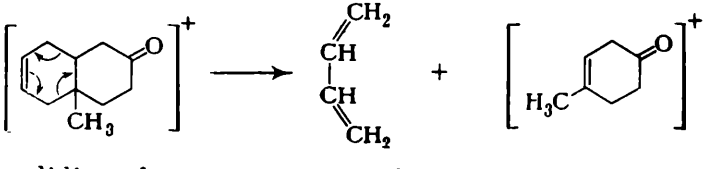


(The transfer of an electron in a homolytic fission of the bond is depicted by a bent full or dashed arrow.)

In the case of amines and amides, analogous rearrangements often proceed via the four-membered transition state (the radical is eliminated as a result of an ordinary α-fission):



The mass spectra of unsaturated polycyclic compounds often involve the peaks of fragments that are formed by a fragmentation which is the converse of diene synthesis (**retrodiene fragmentation**). An example is the fragmentation observed in the spectrum of *trans*-10-methyl-Δ^6-octan-2-one:



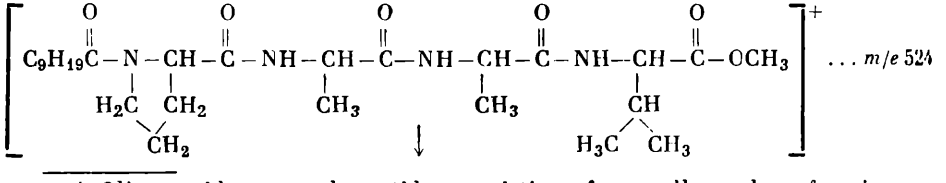
The validity of structures assigned to the fragments formed by the electron impact and their origin from this or that part of the

molecule is confirmed by a comparison with the mass spectra of reference compounds of known structure and by examination of the mass spectra of deuterated analogues. In some cases, compounds are labelled with other stable isotopes (^{18}O, ^{15}O) or chemical labelling is resorted to (e.g., incorporation of CH_3 or OCH_3 groups). The latter procedure, however, is possible only in those cases where there is no risk of a given chemical label causing the change of the fragmentation path.

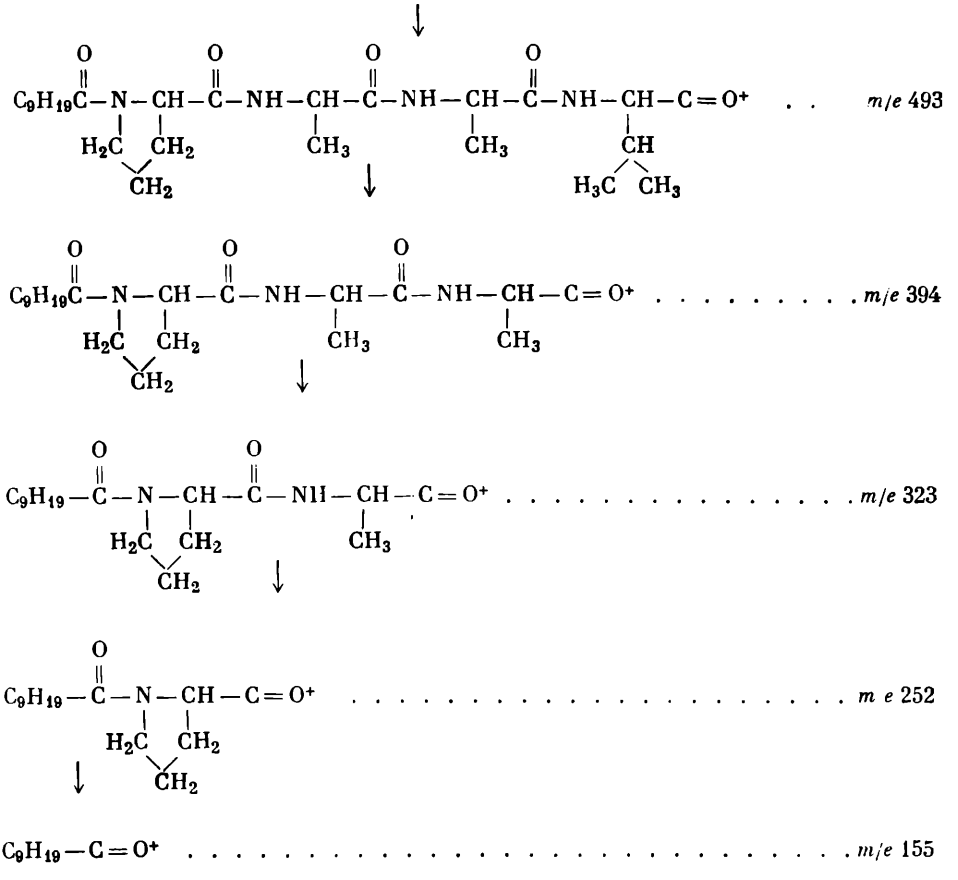
Mass spectrometry is currently very extensively used for elucidating the structure of organic compounds. This method is rapidly developing, embracing nearly all the classes of organic compounds. It is particularly important for the establishment of the structure of complex naturally occurring compounds; in such cases, mass spectrometry enables one to solve complicated problems with a very small amount of compound (fractions of a milligram). The method also finds application in the quantitative analysis of mixtures (especially, those of hydrocarbons).

We shall illustrate the application of mass spectrometry by some examples.

1. **Determination of the Sequence of Amino-Acid Units in Peptides** (E. Lederer, M. M. Shemyakin, N. S. Wul'fson). Owing to the wide application of automatic amino-acid analysers, the determination of the amino-acid composition of peptides presents no serious difficulties today. One of the most important tasks in the elucidation of the primary structure of proteins and peptides—the determination of the amino-acid sequence in the chain—remains, however, to be rather time-consuming and complicated. It has recently been established that when the mass-spectrometric technique is applied to the esters of N-acylated oligopeptides*, the first act of fragmentation of the molecular ion is the elimination of the alkoxy group which results in the formation of a linear ion, whose positive charge is localized at the C-terminal ester bond, and the N-terminal bond is protected by the acyl residue. Further fragmentation of this ion consists in the successive elimination of amino-acid residues with transfer of the positive charge along the chain. For example, the fragmentation of the methyl ester of N-decanoylprolyl-alanyl-alanyl-valine (Fig. 6.5) may be depicted by the following scheme:



* Oligopeptides are polypeptides consisting of a small number of amino-acid units.



Thus, if the amino-acid composition of the oligopeptide under study is known, examination of the mass spectrum permits the determination of the amino-acid sequence in the chain by using only as little as 20-50 μg of the substance. It should be emphasized here that especially good results are obtained if the sample is introduced directly into the ion source and if use is made of high-resolution mass spectrometers.

2. **Elucidation of the Structure of Derivatives of Sugars** (N. K. Kochetkov, O. S. Chizhov). For an organic compound to be amenable to mass-spectrometric analysis, it must be sufficiently volatile; it is for this reason that sugars are converted into their methyl esters or acetates. The molecular ion of a monosaccharide fragments by several routes simultaneously, producing several series of characteristic ions; the most important fragmentation paths for

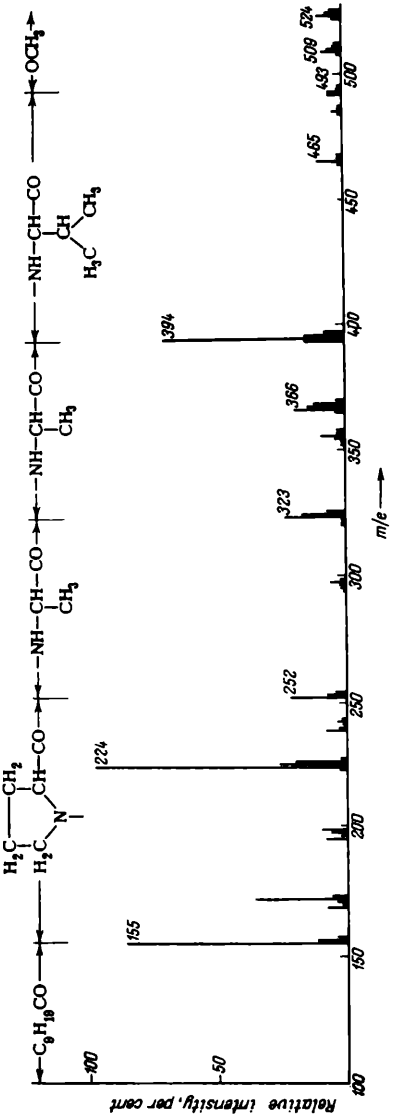
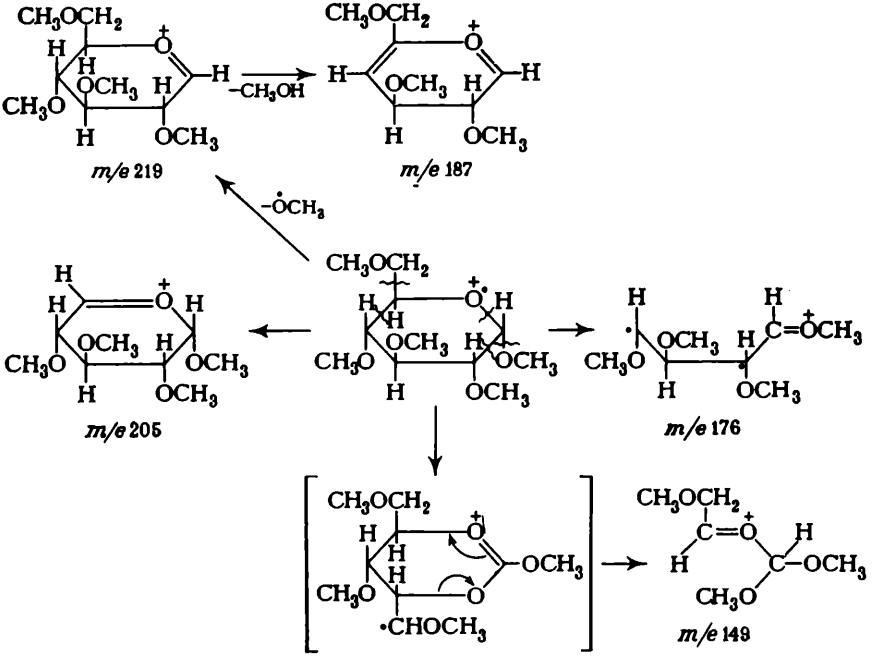


Fig. 6.5.
Mass-spectrum of the methyl ester of N-decanoyl-prolyl-alanyl-valine (fragmentation is given on page 286).

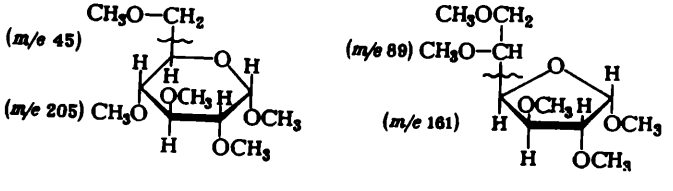
the methyl ester of glucose are presented by the following scheme:



It may be noted, in passing, that nearly all the fragmentations proceed by a single route involving β-fissions, and that the variety of fragmentation routes is due to the large number of functional groups in the sugar molecule.

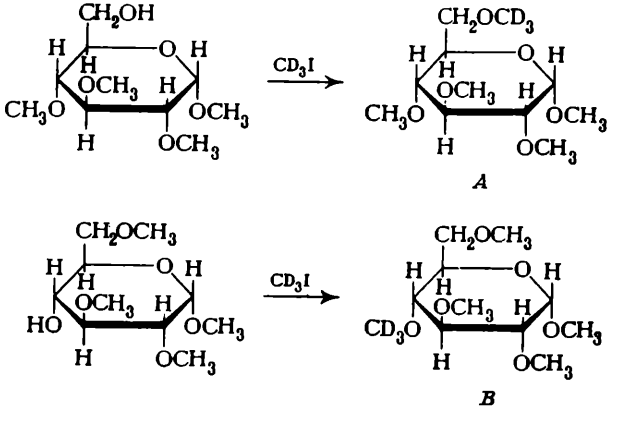
The mass spectrum of a methylated monosaccharide gives, in the first place, information on the number of carbon atoms in the carbon chain of the sugar since an ion of maximum mass number ($M - 31$) is formed when the glycosidic methoxy radical is split off, and has m/e equal to 219 in the case of a hexose. This allows us to assign the sugar to hexoses, pentoses, tetroses, etc.

Furthermore, the mass spectrum makes it possible to measure directly the size of the oxide ring in a sugar derivative since various characteristic peaks are obtained for pyranose and furanose, for example, in the expulsion of the side chain from the ring (β-fission):



If the sugar contains functions other than hydroxyl groups and belongs to the class of amino sugars, deoxy sugars, etc., mass spectrometry makes it possible to determine the location of this substituent and, consequently, to establish the structure of the sugar. For example, the fragmentation of the methyl ester of the N-acetyl derivative of glucosamine gives rise to a number of ions (*m/e* 172, 168, 98), which may result only from the fragmentation of a sugar with the N-acetyl group in the position 2.

It is also possible to determine the structure of numerous sugar derivatives. Of the greatest interest is the elucidation of the structure of partly methylated sugars obtained in the determination of the structure of polysaccharides by the methylation method (page 109). For the disposition of free hydroxyl groups to be determined, a partly methylated monosaccharide is subjected to the action of deuterated methyl iodide, CD_3I, as a result of which the free hydroxyl groups are replaced by the deuteromethoxy groups. For example, the methylglycosides of 2,3,4-trimethylglucose and 2,3,6-trimethylglucose give deuteromethyl derivatives *A* and *B*:



Below are given the values of *m/e* of some peaks in the mass spectra of methylglucosides of 6-deuteromethyl-2,3,4-trimethylglucose (*A*), 4-deuteromethyl-2,3,6-trimethylglucose (*B*) and 2,3,4,6-tetramethylglucose (*C*).

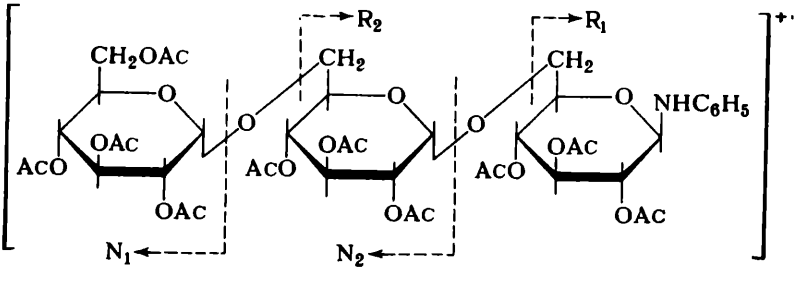
A	222	205	190	176	173	162	152
B	222	208	187	179	173	162	149
C	219	205	187	176	173	159	149

As seen from these data, the mass spectra of two deuterated derivatives are different and differ from the mass spectrum of the nondeuterated tetramethyl derivative of *C* taken for comparison.

The incorporation of three deuterium atoms must increase the *m/e* value of the corresponding ion by three units. Therefore, knowing the structure and origin of the corresponding ion (see the scheme on page 289) and comparing the *m/e* of the peak with that of the undeuterated derivative, we can easily determine at which carbon atom the deuteromethoxy group is located in place of the methoxy group, i.e., to locate the free hydroxyl group in the starting partly methylated sugar. For instance, the ion with *m/e* 205 (see the same scheme) increased by three units for deuterated derivative *B* and remained unchanged for *A*. It is apparent that in the second case the deuteromethoxy group was split off. But we know that this ion is formed when carbon atom 6 and the methoxy group attached to it are eliminated; hence, the deuterated derivative *A* contained the deuteromethoxy group at C_6. On the contrary, the ion with *m/e* 187 retained its value in the case of deuterated methyl derivative *B* and increased by three units for *A*. At the same time we know that the ion with *m/e* 187 is formed as a result of the splitting-off of the methoxy group at C_4. Hence, deuterated derivative *B* contained a deuteromethoxy group at carbon 4. From this we can draw a conclusion as to the sites of free hydroxyls in the starting partially methylated derivatives.

Mass-spectrometric analysis enables us to solve more complicated problems in the investigation of carbohydrates. For example, on the basis of mass-spectral data alone it is possible to determine the structure of disaccharides since a number of peaks in the mass spectra of disaccharides with different types of bond between the monosaccharides can be differentiated.

It has recently become possible to apply mass-spectrometric analysis to the solution of a complicated problem—the elucidation of the structure of oligosaccharides, for which purpose less than 1 mg of substance is required. An oligosaccharide in the form of acetate is treated with aniline to convert it into the anilide, which is subjected to mass-spectrometric analysis. The anilide which has an aromatic system gives a stable molecular ion on electron bombardment,



which then undergoes fragmentation with the subsequent elimination of the monosaccharide units from the reducing end (series R) or from the non-reducing end of the chain (series N). From the *m/e* value of the fragments formed we can establish the sequence of monosaccharide units in the oligosaccharide chain. The resulting primary fragments break down into smaller fragments, the structure of which depends on the type of glycosidic linkage. This permits us to elucidate not only the sequence of monosaccharide units in the chain but also the nature of the bond between them by differentiating 1 → 6 bonding units from 1 → 4 bonds, etc.

Thus, by using mass spectrometry alone we can establish the entire structure of oligosaccharides.

Below are given the values of *m/e* for some characteristic peaks of methylated isomeric glucosylglucoses containing 1 → 6 and 1 → 4 bonds:

Gentiobiose (1 → 6 bond)	—	353	—	—
Cellobiose (1 → 4 bond)	380	—	305	161

From these data it is seen that on the basis of mass spectra we can differentiate between gentiobiose (1 → 6 bond) and cellobiose (1 → 4 bond), etc. Differences in the mass spectra arise from the different routes of fragmentation of disaccharides caused by the breakdown of the reducing monosaccharide unit since this unit is replaced by the non-reducing monosaccharide in different positions—at carbon atoms 6, 4, etc.

(B) Nuclear Magnetic Resonance

A little more than 20 years have elapsed since the discovery of the phenomenon of nuclear magnetic resonance (NMR). During this relatively short period **nuclear magnetic resonance spectroscopy** has become one of the principal techniques for the investigation of organic molecules. Nuclear magnetic resonance spectroscopy provides considerably more information than any other spectroscopic method or mass spectrometry. The use of NMR spectroscopy makes it possible to study the structure of molecules, their conformation, electron-density delocalization, weak intermolecular interactions (complex formation, solvation, hydrogen bonds), hindered internal rotation, tautomeric equilibrium, and sometimes also the kinetics of reactions. We shall consider only the simplest conceptions and examples of application of the method.

The Spectroscopic Method (NMR). Many atomic nuclei have a spin magnetic moment associated with the spinning of an atomic charge about the nucleus axis. According to the magnitude of the

spin quantum number I, atomic nuclei may be subdivided into the following groups:

(a) $I = 0$ (no spin moment) . . . . ^{12}C, ^{16}O, ^{28}Si

(b) $I = \frac{1}{2}$ . . . . . ^{1}H, ^{3}H (tritium), ^{13}C, ^{19}F, ^{31}P

(c) $I = 1$ . . . . . ^{2}H (deuterium), ^{14}N

(d) $I = \frac{3}{2}$ . . . . . ^{11}B, ^{35}Cl, ^{37}Cl, As

(e) Nuclei with higher values of I.

The examples given include only those nuclei which are most important to organic chemistry.

Nuclei with a spin of $I = 0$ have no magnetic moment and are insensitive to the NMR method. Nuclei with a spin of $\frac{1}{2}$ are most convenient for investigations by this technique. Protons and nuclei of ^{19}F are particularly highly sensitive. Nuclei with spins higher than $\frac{1}{2}$ possess an electric quadrupole moment in addition to the spin magnetic moment. The presence of the quadrupole moment considerably complicates the observation of NMR signals, but such nuclei can be studied by the **nuclear quadrupole resonance** (NQR) method. The NQR method is of less importance to organic chemistry and is not discussed in this book. Hydrogen nuclei, or protons, are mainly used in NMR studies since they are present in nearly all organic molecules and also because they are highly sensitive to the method. In what follows we are exclusively concerned with **proton magnetic resonance** (PMR).

If a nucleus with a magnetic moment μ and a spin quantum number I is placed in an external magnetic field H_0, then, according to the principles of quantum mechanics, the magnetic moment may assume $2I + 1$ stable orientations with respect to the direction of the applied field H_0. Thus, for the proton, $\left(I = \frac{1}{2}\right)$, there are only two orientations possible—lined up with the direction of the field H_0 (parallel orientation), $m = +\frac{1}{2}$, or lined up against the direction of the field (antiparallel orientation), $m = -\frac{1}{2}$. Thus, protons when placed in an external magnetic field occupy two energy levels with energies $E_1 = +\mu H_0$ and $E_2 = -\mu H_0$. The parallel orientation of the magnetic moment is more favourable (stable), the difference between the energy levels being equal to

$$\Delta E = 2\mu H_0 \tag{1}$$

The energy difference ΔE depends only on the strength of the applied field H_0 and can be estimated by substituting into expression (1) the μ value of the proton (1.42×10^{-23}) and the magnetic

field strength in gauss, say, 10,000 gauss:

$$\Delta E = 2 \cdot 1.42 \cdot 10^{-23} \cdot 10^4 = 2.84 \cdot 10^{-19} \text{ ergs}$$

that is, the energy difference is very small. Nevertheless, if there were no thermal motion, all the protons would be at the lower energy level. The energy of thermal motion, however, tends to bring the "populations" of the levels into accord with Boltzmann's law:

$$\frac{N_1}{N_2} = e^{\frac{\Delta E}{kT}} \tag{2}$$

where N_1 and N_2 are the number of molecules at the respective energy levels. With the given value of H_0, this ratio is about 1.000007 at room temperature (i.e., if the higher energy level contains 1,000,000 protons, the lower level has 7 protons more). The difference between the populations of the levels is negligible but it nevertheless exists and the system of protons being in a magnetic field is capable of absorbing small quanta for the following condition to be fulfilled:

$$h\nu = 2\mu H_0 \tag{3}$$

This corresponds approximately to metre electromagnetic waves. The resonance frequencies for protons are as follows: 42 megacycles per second with a magnetic field of 10,000 gauss; 60 Mcps for 14,000 gauss; 100 Mcps for 24,500 gauss. It is important to note that the resonance frequencies for different nuclei (^{1}H, ^{19}F, ^{31}P, etc.) sharply differ from one another and their spectra never overlap.

Thus, the frequency at which absorption takes place is called the **resonance frequency**, and the phenomenon itself is known as **nuclear magnetic resonance**. As the frequency of the electromagnetic field deliberately imposed on the sample is gradually changed the absorption begins at a certain value of ν. The absorption intensity depends on the concentration of protons in the sample. On further increase of the frequency the quantum energy goes beyond the required value and the absorption stops. Consequently, the NMR spectrum must have the form of a narrow peak.

In practice, NMR spectra are obtained as follows. The substance contained in a cylindrical sample tube is placed between the pole pieces of an electromagnet (Fig. 6.6), which produces a uniform constant high-strength field. A radiofrequency field is applied by passing an alternating current through a coil which is wound around the sample tube. Further, theoretically it is immaterial whether we vary gradually the frequency of this electromagnetic field, ν, at a constant magnetic field H_0, or, on the contrary, H_0 is gradually varied at constant ν. Both types of instruments are available. If the magnetic field strength H_0 is varied then at a certain value of H_0 the sample absorbs the energy, and the current flow in the coil falls off. This variation is amplified and transmitted to the recorder or oscillograph.

Usually, the spectra of liquids or solutions are taken, sometimes those of gases. In crystals, the magnetic moments of nuclei are affected by the spatially fixed magnetic moments of neighbouring nuclei and the absorption bands obtained are blurred, the effect produced being similar to using an inhomogeneous field. In liquids, the effect

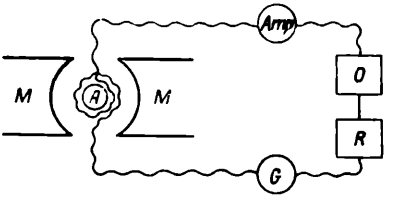


Fig. 6.6.

Schematic representation of NMR instrument:
A— ampoule with sample; *M*— magnet; *G*— generator; *Amp*— amplifier; *O*— oscillograph. *R*— recorder.

of neighbouring nuclei is averaged out to zero by rapid random molecular motions. Of course, the solvents used must be liquids which do not give NMR spectra (CCl_4, CS_2) or those absorbing in a different region ($CDCl_3$).

Nuclear magnetic resonance instruments are characterized by three main parameters: the working frequency (40, 60, and 100 Mcps), which depends on the magnetic field H_0 in the magnet; sensitivity and resolving power. The higher the sensitivity of the instrument the more intensive the signals, with the same concentration of protons in the sample. Current instruments allow us to distinguish between two lines which are only 0.2-0.5 cps apart from each other. The **resolving power** is defined as the ratio of this minimum distance (when the lines can be distinguished as distinct lines) to the working frequency of the instrument expressed in cycles per second (cps). The resolving power of the most efficient instruments operating at a frequency of 100 Mcps is as follows:

$$\frac{0.2 \text{ cps}}{10^8 \text{ cps}} = 2 \times 10^{-9}$$

The resolution of the spectrum is of course impaired as the lines are broadened. The resolution of the spectra depends on the resolving power of the instrument, the velocity of spectrum scanning and on the properties of the sample (for example, on the viscosity of the solution).

The Chemical Shift. From what has been said above it might be expected that the nucleus of one and the same isotope, say, the proton, would invariably give the same peak in the NMR spectrum. It is because in the equation $h\nu = 2\mu H$ the quantities h and μ are

constant and ν and H are also constant when the resonance is attained. But the atomic nuclei in molecules are surrounded by electrons which shield them from the action of the magnetic field H_0. Therefore, the magnetic field which a proton truly experiences is not simply the external field applied H_0 but rather the somewhat lower field H_{eff}:

$$H_{eff} = H_0 - \sigma H_0 = (1 - \sigma) H_0 \qquad (4)$$

The coefficient σ is known as the **shielding constant** of a given proton in a given molecule. The values of σ are not great for protons (they are of the order of 10^{-6} and somewhat greater for other

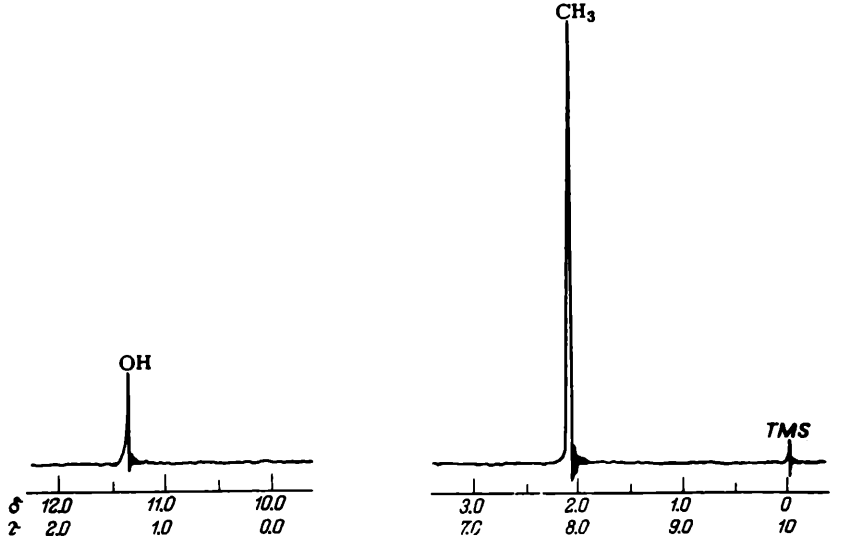


Fig. 6.7.

NMR (PMR) spectrum of acetic acid at a generator frequency of 40 megacycles per second (δ and τ scales are given).

nuclei). The shielding constant is therefore a function of the molecular environment of the proton affording the signal, and is largely determined by the density of the surrounding electron cloud. The electron-attracting groups and atoms adjacent to the proton reduce the density of the electron cloud and the shielding constant, and the resonance therefore occurs at a lower, modified magnetic field H_0. The most common electron-attracting groups are NO_2, F, Cl, CN, OR, COOR. The reverse effect is exhibited by electron-releasing groups.

Figure 6.7 shows the spectrum of acetic acid. It consists of two signals due to the two types of hydrogen atoms in the molecule.

The signal in the lower field corresponds to the hydrogen atom of the carboxyl group. The distance between the two signals, which can be measured in terms of frequency or magnetic field units, is called the **chemical shift**. The shielding effect σH_0 is proportional to the magnetic field strength H_0, and therefore the magnitude of chemical shifts, expressed in frequency or magnetic field units, will also be dependent on H_0. To facilitate comparisons between chemical shifts measured

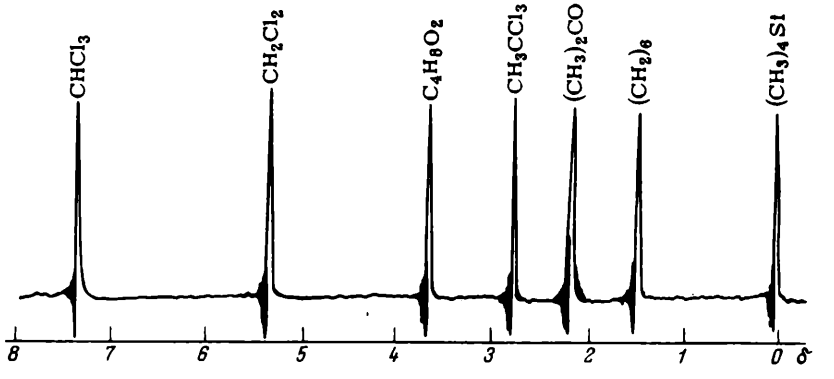


Fig. 6.8.
NMR spectrum of a mixture of compounds.

at different frequencies, chemical shifts are recorded as fractions of the field strength or frequency, this ratio being then multiplied by 10^6. The chemical shift between two protons, A and B, will thus be equal to

$$\delta_{AB} = 10^6 \cdot \frac{H_A - H_B}{H_0} = \frac{\nu_A - \nu_B}{\nu_0} \cdot 10^6 \qquad (5)$$

where ν_A and ν_B are the values of resonance frequency for protons A and B, and ν_0 is the spectrometer frequency.

The chemical shift δ_{AB} is no longer dependent on H_0 and is measured in dimensionless units—in parts per million (ppm).

If we have a mixture of compounds, each of which has protons of only one kind, the spectrum of this mixture will contain the same number of single narrow lines as there are compounds in the mixture. Figure 6.8 gives the spectrum of a mixture of tetramethylsilane, cyclohexane, acetone, 1,1,1-trichloroethane, dioxan, methylene chloride and chloroform. It is easy to see that the chemical shifts are in good agreement with the concepts of the electron-attracting power of the atoms and groups with which the proton is bound. It is convenient to measure chemical shifts relative to some arbitrary standard which contains the nucleus under consideration. A common practice is to use tetramethylsilane (TMS) as a reference compound,

a small amount of which is added to the sample tube. The TMS narrow intense line is at a higher field than the signals of hydrogen atoms in most of the common organic compounds, and besides, TMS is chemically inert.

At present, there are two scales for measuring chemical shifts—the delta (δ) scale and the tau (τ) scale. In both scales, chemical shifts are measured in parts per million (ppm) and the reference compound is tetramethylsilane (TMS). The difference between these scales is that the TMS signal is at 0 on the δ-scale and at 10 ppm on the τ-scale, i.e.,

$$\delta = \frac{H_{TMS} - H_X}{H_{TMS}} \times 10^6$$

$$\tau = \left[10 - \frac{H_{TMS} - H_X}{H_{TMS}} \times 10^6\right]$$

$$\tau = 10 - \delta \qquad (6)$$

The area under the peak curve in the NMR spectrum is proportional to the number of nuclei of a given species in the sample. For example, in acetic acid (see Fig. 6.7) the ratio of the areas (which can be determined graphically or with the aid of an electronic integrator) is 3 : 1. Owing to this, NMR spectra may be used for quantitative analysis of mixtures. For example, in Fig. 6.8 the intensities of all the signals are identical, and the concentrations of the components in the mixture are therefore inversely proportional to the number of equivalent protons contained in their molecules, namely:

$$[C_6H_{12}]:[C_3H_6O]:[CH_3CCl_3]:[C_4H_8O_2]:[CH_2Cl_2]:[CHCl_3] = 2:4:8:3:12:24$$

Thus, each kind of proton has a chemical shift of its own. It has been demonstrated with a large number of examples that the protons of isostructural fragments of different molecules give resonance signals in a constant narrow region of the spectrum. This enables using NMR data for obtaining information on the structure of molecules. The interpretation of NMR spectra is greatly assisted by determination of line intensities and analysis of the fine structure of lines due to spin-spin interactions of protons with protons on adjacent carbon atoms.

Table 6.3 lists the approximate values of chemical shifts for protons on carbon atoms in different environments. It is seen that, first, the shielding effect increases in going from the methine to methylene to methyl group (compare the data in different columns in the same rows); this corresponds to a decrease in the chemical shift on the δ-scale. Second, the magnitude of chemical shift depends essentially on the nature of the substituent. This can be traced out for the aldehyde group in aromatic compounds. With decreasing electron-attracting ability of the substituent in the *para*-position of benzaldehyde

the signal produced by the proton of the CHO group is shifted to a region of higher fields.

TABLE 6.3. **The Chemical Shifts of Protons on the δ-Scale (those enclosed in parentheses are τ values)**

1. Protons of CH_3, CH_2 and CH groups bound to different groups Y

Y	CH_3Y	RCH_2Y	R_2CHY
R (alkyl)	0.90 (9.10)	1.25 (8.75)	1.50 (8.50)
$CH_2=CH$	1.70 (8.30)	1.90 (8.10)	—
COOR	2.00 (8.00)	2.10 (7.90)	—
CN	2.00 (8.00)	—	—
COOH	2.07 (7.93)	2.34 (7.66)	—
CHO	2.17 (7.83)	2.20 (7.80)	—
NR_2	2.15 (7.85)	2.50 (7.50)	2.87 (7.13)
I	2.15 (7.85)	3.15 (6.85)	4.20 (5.80)
C_6H_5	2.34 (7.66)	2.62 (7.38)	2.87 (7.13)
Cl	3.05 (6.95)	3.40 (6.60)	4.00 (6.00)
OR	3.30 (6.70)	3.35 (6.65)	3.80 (6.20)
OH	3.38 (6.62)	3.56 (6.44)	3.85 (6.15)
OCOR	3.65 (6.35	4.15 (5.85)	5.01 (4.99)
OC_6H_5	3.70 (6.30)	3.90 (6.10)	—
$OCOC_6H_5$	3.90 (6.10)	4.23 (5.77)	5.12 (4.88)

2. Protons of the aldehyde group

p-$C_6H_4(CHO)_2$	10.08(−0.08)
C_6H_5CHO	9.965 (0.035)
p-ClC_6H_4CHO	9.933 (0.67)
p-$CH_3C_6H_4CHO$	9.98 (0.02)
CH_3CHO	9.72 (0.28)

3. Protons of some aromatic compounds

Pyridine (-2)	8.50 (1.50)
p-$C_6H_4(CHO)_2$	7.54 (2.46)
Benzene	7.27 (2.73)
Toluene	7.10 (2.90)
p-Cresol	6.75 (3.25)
Pyrrole (-3)	6.09 (3.91)

Spin-Spin Interaction. Only in rare cases are NMR spectra so simple as the spectrum of acetic acid shown in Fig. 6.7. As a result of the interaction between the closely spaced protons of the same molecule, the observed absorption bands very often appear, not as single, sharp peaks in the recorded NMR spectrum, but as groups of separate peaks, i.e., they exhibit a fine structure. Figure 6.9 shows the spectrum of ethylbenzene at different resolutions. At a higher resolution the band corresponding to the methylene protons is split into four lines (a quadruplet), and the band of the methyl protons appears as a set of three lines (a triplet). **Spin-spin interaction** (or *spin-spin coupling*) consists in the following: the magnetic moment of the neighbouring proton (or any other nucleus possessing a magnetic moment) modifies somewhat the effective magnetic field H_{eff} at the proton or group of equivalent protons under consideration, so that it is not exactly the same as the applied field. Let us consider a molecule with two different interacting protons, A and B. In the external magnetic field, the proton A may have only two orientations:

alignment with the field $\left(\text{spin } +\frac{1}{2}\right)$ and against the field $\left(-\frac{1}{2}\right)$. The proton B will thus be influenced in one case by the field $H_{\text{eff}} - a$, and in the other, by $H_{\text{eff}} + a$, where a is the correction introduced by the magnetic moment of the nucleus A. Since the sample contains practically the same number of protons A opposing and reinforcing the field, a set of two lines of equal intensity (a doublet) will appear in the spectrum; the signal of the proton A on nucleus B will be split in the same way. Let us now examine a more complicated case, namely, the spectrum of the ethyl group of ethylbenzene, whose protons do not interact with the ring protons. Thus, apart from the effective magnetic field, the methyl protons are subjected to the net action of the methylene protons. The total spin of the methylene group may assume three values:

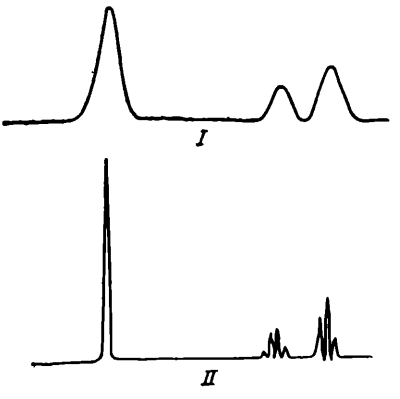


Fig. 6.9.

NMR spectra of ethylbenzene:
I— at a frequency of 40 Mcps and a resolution of 10^{-6}; *II*— at the same frequency and a resolution of 10^{-8}.

$$+1/2+1/2=+1 \qquad +1/2-1/2=0 \qquad -1/2+1/2=0 \qquad -1/2-1/2=-1$$

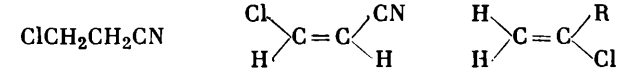
According to what has been said, the methyl proton signal must be split into three lines, and the medium line must be twice as intensive as either of the other two (see Fig. 6.9) since the net zero spin is twice as probable. An analogous examination of the spin states of the methyl protons leads to the conclusion that the signal of the methylene group must be a quadruplet with line intensities in the ratio of 1 : 3 : 3 : 1, which is actually observed.*

Generally speaking, if a proton or group of equivalent protons is involved in a spin-spin interaction with n equivalent protons, then

* The distribution of the spins of the methyl protons is as follows: $+\frac{1}{2}+\frac{1}{2}+\frac{1}{2}=+1\frac{1}{2}$; $+\frac{1}{2}+\frac{1}{2}-\frac{1}{2}=\frac{1}{2}$; $+\frac{1}{2}-\frac{1}{2}+\frac{1}{2}=+\frac{1}{2}$; $-\frac{1}{2}+\frac{1}{2}+\frac{1}{2}=+\frac{1}{2}$; $-\frac{1}{2}-\frac{1}{2}+\frac{1}{2}=-\frac{1}{2}$; $-\frac{1}{2}+\frac{1}{2}-\frac{1}{2}=-\frac{1}{2}$; $+\frac{1}{2}-\frac{1}{2}-\frac{1}{2}=-\frac{1}{2}$; $-\frac{1}{2}-\frac{1}{2}-\frac{1}{2}=-1\frac{1}{2}$. Thus, the values of the net spin moment equal to $+\frac{1}{2}$ and $-\frac{1}{2}$ are three times more probable than the values $+1\frac{1}{2}$ and $-1\frac{1}{2}$.

its signal will consist of $n + 1$ lines. The spacing between the nearest lines of the multiplet is strictly identical. This spacing measured in cycles per second is called the **spin-spin coupling constant** and is denoted by the symbol J. It is important to note that J is the same in both multiplets of two groups of interacting nuclei (J is the same in the triplet and quadruplet of ethylbenzene). The multiplet is always symmetrical with respect to the centre, from which the chemical shifts are measured.

It is necessary to remember that spin-spin splitting is observed only between magnetically non-equivalent nuclei, which are chemically also non-equivalent. For example, there is always such an interaction between the protons and nuclei of ^{19}F or ^{31}P (the spin of all these nuclei is $\frac{1}{2}$). There is no spin-spin interaction between protons in CH_2Cl_2, $ClCH_2CH_2Cl$, cyclobutane, $ClCH{=}CHCl$. Spin-spin interaction occurs, for example, in the following cases:



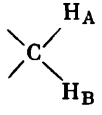
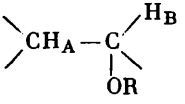
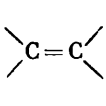
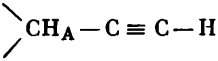
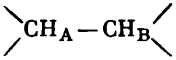
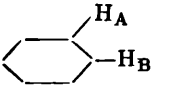
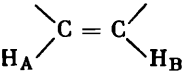
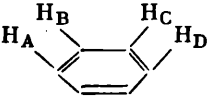
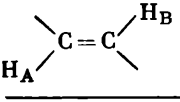
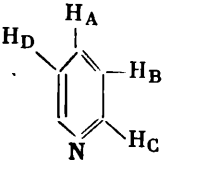
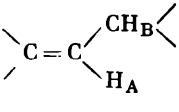
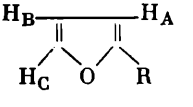
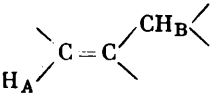
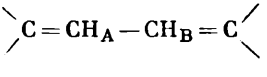
In the first two compounds the protons on adjacent carbon atoms are non-equivalent because different groups are attached to these carbon atoms. In the last example, the presence of non-equivalent protons is accounted for by their different geometric position relative to the substituent at the adjacent carbon atom.

Spin-spin interaction is transmitted by the electrons of chemical bonds, and therefore the quantity J is dependent on the number of bonds separating the interacting nuclei, and also on the nature of these bonds. For example, in the series $FHCCl_2$, $HCCl_2CCl_2F$, $HCCl_2CCl_2CCl_2F$, the spin-spin coupling decreases in that order and in the last case the quantity J_{HF} is negligibly small. Spin-spin interaction is transmitted through triple bonds more effectively than through double bonds, and more strongly through double than single bonds; with a double bond, *trans*-protons have a higher J than *cis*-protons. The axial-axial spin-spin interaction is stronger than the axial-equatorial and equatorial-equatorial interactions. The characteristic values of J are presented in Table 6.4.

In contrast to chemical shifts (expressed in cycles per second), the magnitude of the spin-spin coupling constant does not depend on the applied magnetic field strength H_0, and therefore, when measurements are made in different fields, it is easy to decide whether the lines are associated with a spin-spin interaction or present independent signals.

Spin-spin splitting provides highly valuable information on molecular structure, but, on the other hand, it greatly complicates the

TABLE 6.4. Characteristic Values of Spin-Spin Coupling Constants for Selected Compounds

Fragment	J, cps	Fragment	J, cps
	12-15		1-3
	0.35-2		2-3
	2-9		J_{aa} 9-13 J_{ae} 2-4 J_{ee} 2.7-4
	6-14		J_{AB} 7-10 J_{AC} 2-3 J_{AD} <1.5
	11-18		J_{AB} 7.5-8 J_{AC} 1.4-2 J_{BC} 5.2-5.5 J_{CD} 0.9
	4-10		J_{AB} 3-4 J_{AC} 0.6-1 J_{BC} 1.8-2
	0.5-2		
	10-13		

general pattern of the spectrum. In dealing with complicated NMR spectra it is sometimes necessary to eliminate the spin-spin interaction at some portion of the spectrum in order to simplify it. In current NMR instruments, this can be done with the aid of the "double resonance" method.

Unfortunately, NMR spectra are easily interpreted only in those cases when the spin-spin splitting constant J is considerably (by several times) lower than the chemical shifts between the interacting nuclei. Such spectra are called **first-order spectra.** If, however, the values of these quantities are close, the spectra are often complicated to such an extent that their interpretation is possible only with the aid of electronic computers. A complicated spectrum can occasionally be reduced to a first-order spectrum by studying the sample on an instrument with a higher input frequency. The replacement of

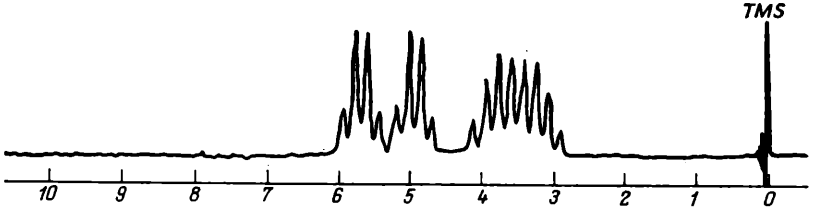


Fig. 6.10.

NMR (PMR) spectrum of the compound $(CF_3)_2CH—CF=CH—CF_3$ at a generator frequency of 40 Mcps.

one or more protons by deuterium makes it possible to simplify the spectrum considerably. Since the spectra of different isotopes are never overlapped, the signals of the protons being replaced disappear. The spin-spin coupling constant J for a proton and a deuterium nucleus is 7 times lower than in the case of the interaction between two protons in the same positions; the multiplet structure therefore disappears. It is interesting that an examination of the NMR spectrum of a partly deuterated compound may provide a clue as to the position of deuterium in the molecule and, often, also the percentage of deuteration.

Some examples of the use of NMR (PMR) spectra are given below.

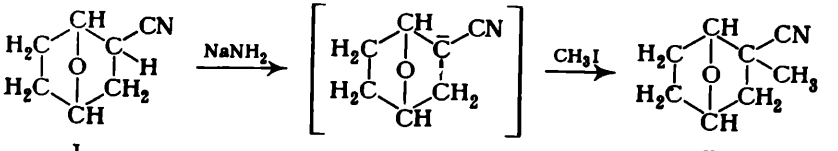
Example 1. The elimination of hydrogen chloride from $(CF_3)_2CH—CFCl—CH_2CF_3$ gives a compound to which either of the following two formulas may be assigned:

$$\underset{\text{I}}{(CF_3)_2C=CFCH_2CF_3} \qquad \underset{\text{II}}{(CF_3)_2\overset{\text{A}}{C}H\overset{\text{B}}{C}F=CHCF_3}$$

The proton magnetic resonance spectrum (Fig. 6.10) shows that formula II holds true. Recall that the nuclei of F have a spin of $\frac{1}{2}$, but their signals in the NMR spectrum lie in an entirely different region than the proton signals. The spin-spin interaction between ^1H and ^{19}F is of the same order as that between the protons. Formu-

la I is discarded since otherwise the spectrum must contain two equivalent protons and hence one multiplet (consisting of 8 lines) must correspond to it. There are in fact two multiplets. The multiplet of proton B must contain eight lines (the splitting of the signal on the three fluorine nuclei of the CF_3 group and of each of these signals on the fluorine nucleus of the —CF group). In the multiplet A there must be 14 lines, but not all the lines are seen in the spectrum because the extreme lines of the multiplet are only slightly intensive.

Example 2. When nitrile I was alkylated by methyl iodide (after compound I was treated with sodium in liquid ammonia), nitrile II was expected to result:



I II

The reaction, however, gave a compound of the composition $C_9H_{13}NO$, whose PMR spectrum is given in Fig. 6.11. The intensive singlets undoubtedly belong to two different methyl groups. This

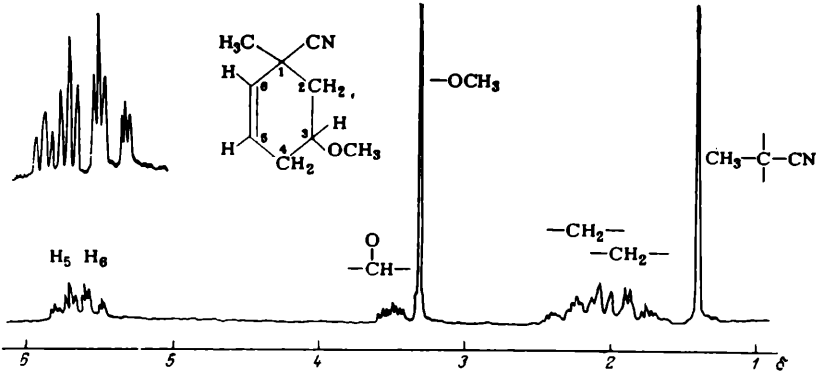


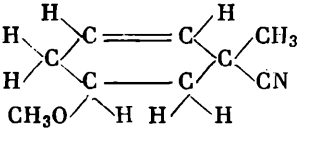
Fig. 6.11.

PMR spectrum of the nitrile of 1-methyl-3-methoxycyclohexene-5-carboxylic acid (III) at a generator frequency of 100 Mcps (10-percent solution in CCl_4).

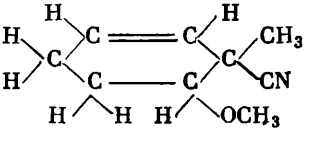
can be deduced from the signal intensities and chemical shifts. The signals of the more strongly deshielded protons, i.e., those of the methyl group linked to an electronegative atom (oxygen), must be at low fields. It is thus clear that the double methylation of the

starting compound with the rupture of the bridge linkage has taken place; also this is in agreement with the formula $C_9H_{13}NO$. On the basis of the chemical shift and the relative intensity of the signal it may be stated that the multiplet at $\delta = 5.6$ ppm corresponds to the protons at the double bond (the signals of such protons always lie at lower fields than those of the protons on the saturated carbon atoms). Additional explanations are required for further interpretation of this portion of the spectrum. If only two protons were interacting and the chemical shift difference were considerably larger than J, then the spectrum would consist of two separate doublets and the intensities of all the four lines would be identical (a spectrum of the AX type). If, however, $\Delta\delta$ and J were of the same order of magnitude, then the external components of the spectrum would be less intensive than the internal components (a spectrum of the AB type). The resulting spectrum differs from the latter only in that each line is split into three lines more. This means that both protons situated at the double bond enter into spin-spin interaction with only two equivalent protons (those of the CH_2 group). From what has been said above we may suggest two structural formulas for the resulting compound—III and IV:

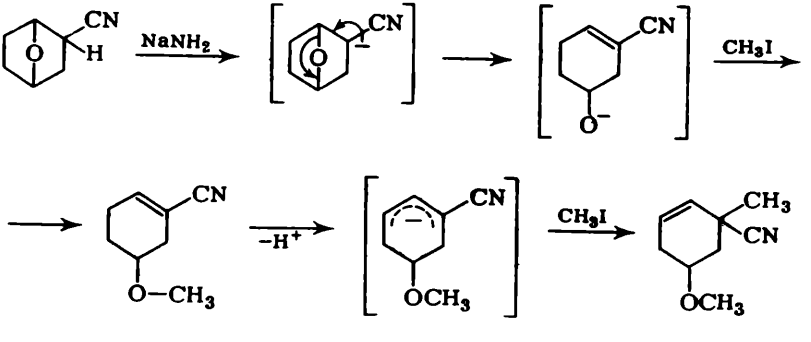
III



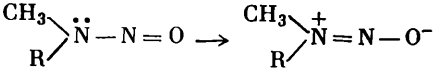
IV



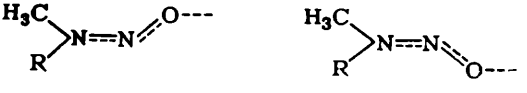
The choice between these structures has been made on the basis of the multiplet produced by the methine proton (3.45 ppm). In structure IV the signal of this proton must contain three lines (if the protons of the adjacent methylene group are equivalent) or four lines as a maximum (if they are non-equivalent because of the different position relative to the OCH_3 group); hence, formula IV may be discarded. The mechanism of the formation of compound III may be represented as follows:



Example 3. The delocalization of electron density in nitrosamines must be intermediate between the two limiting formulas:



Because of the partial doubling of the N=N bond there may exist stable conformations of the *syn-* and *anti*-types:



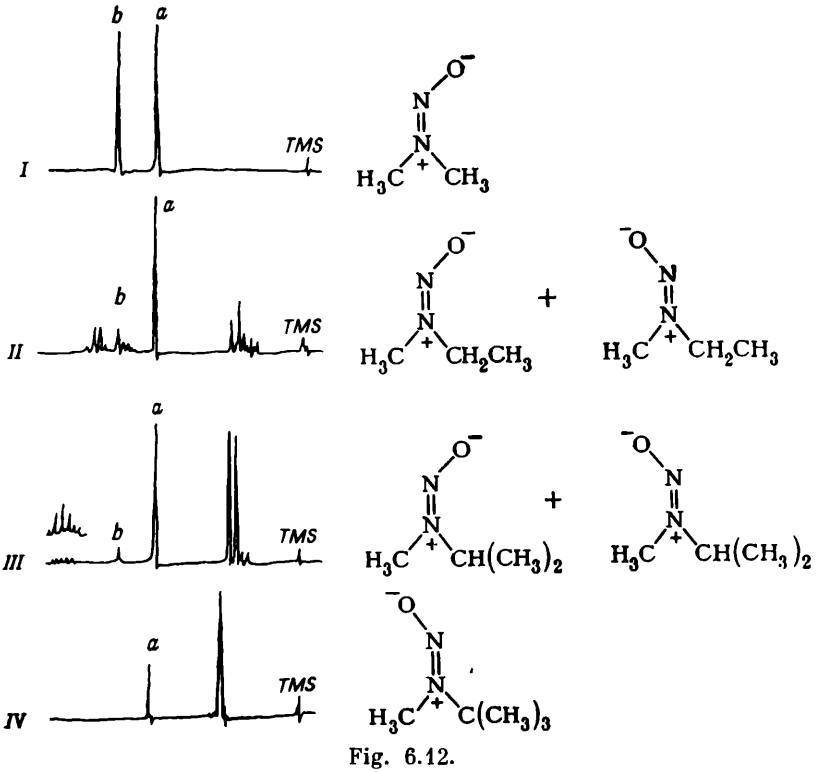


Fig. 6.12.

PMR spectra of nitrosamines at a generator frequency of 60 Mcps:
I— dimethylnitrosamine; *II*— methylethylnitrosamine; *III*— methylisopropylnitrosamine; *IV*— methyl-*tert*-butylnitrosamine.

With the aid of NMR spectra it has been shown that this is actually the case, and the ratio of the conformations, depending on the volume of substituent R, has been established.

The spectra of four nitrosamines have been taken; the bulk of R gradually increases in the following sequence: CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$.

In the case of dimethylnitrosamine, two sharp peaks of equal intensity are observed in the PMR spectrum (Fig. 6.12, *I*). This means that the methyl groups are non-equivalent (due probably to the restricted rotation about the N=N bond).

The spectrum of methyl-*tert*-butylnitrosamine (IV) also contains two peaks: one intensive (the protons of the tertiary butyl group) and the other less intensive (the protons of the single methyl group). The more bulky *tert*-butyl group must be in the *anti*-position relative to the oxygen. Because of the steric hindrances the second possible conformation is unfavourable and is not observed in the PMR spectrum.

From the other two spectra it follows that in the case of nitrosamines in which R = $-C_2H_5$ (spectrum II) and $-CH(CH_3)_2$ (spectrum III) the compounds are represented by a mixture of two non-equivalent conformations. The ratio of the areas of the peaks *a* and *b* in each of these spectra is equal to the ratio of the number of molecules in each of the conformations (these are the signals of the methyl protons in different conformations). The more bulky is the substituent R, the smaller is the contribution of the conformation with this substituent being in the *syn*-position relative to the oxygen. This can also be deduced from the relative intensity of the signals from the protons of the ethyl and isopropyl groups in different conformations.

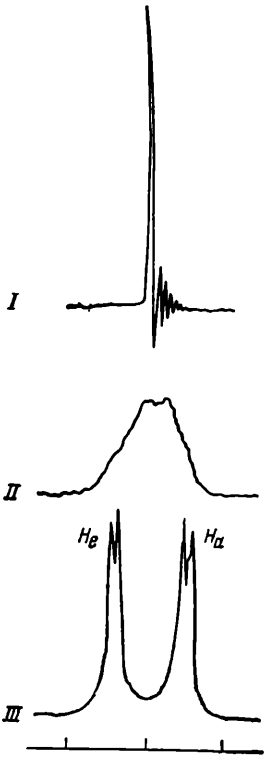


Fig. 6.13.

PMR spectra of cyclohexane at a generator frequency of 100 Mcps and at temperatures: +20°C (*I*), −30°C (*II*), −100°C (*III*).

Example 4. A study of the conversion of cyclohexane (Fig. 6.13). The cyclohexane molecule has the stable chair conformation. Accordingly, the molecule must contain two types of proton—axial and equatorial protons. At room temperature, however, the PMR spe-

ctrum contains only one sharp singlet. This is associated with the very rapid flipping of one chair conformation of the ring to the other chair form, so that the axial and equatorial protons are constantly exchanged. At lower temperatures (a solution of cyclohexane in carbon disulphide), beginning with —30°C, the signal is broadened, and at —100°C two distinct signals and their fine structure are seen, the fine structure being due to the spin-spin interaction. By studying the temperature relationships of such transfers it is possible to calculate the energy barriers for such conformational changes.

(C) Optical Spectroscopy in Organic Chemistry

All spectroscopic methods are based on the measurement of the relation between the intensity of absorption, emission or scattering of light and the light frequency (or wavelength). In optical spectroscopy, use is made of absorption spectra in the infrared, visible or ultraviolet regions in the range of wavelengths from 10^{-1} to

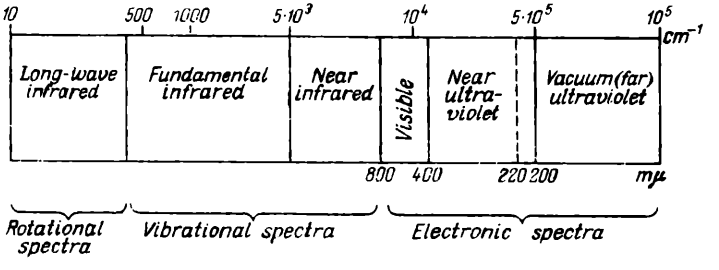


Fig. 6.14.
The optical spectrum regions.

10^{-6} cm^{-1}, and also of combination-scattering (Raman) and luminescence spectra (the less important and general luminescence method is not discussed here). Figure 6.14 gives a classification of spectra based on the wavelength (or frequency). The resolution of an optical spectrum into these regions is associated with the resolving power of instruments and also with the nature of light absorption in different regions. Of particular interest to the organic chemist are: the near-ultraviolet and visible (from 220 to 800 nm*), and fundamental infrared (from 5000 to 200 cm^{-1}) regions.

The principle of measurement of optical spectra is very simple. A beam of monochromatic light, whose wavelength is gradually

* The abbreviation nm stands for nanometer, 1 nm = 1 mμ (millimicron) = = 10 Å = 10^{-7}.

changed with the aid of a special instrument called a monochromator, is allowed to pass through a layer of a substance (more often in solution).

The intensity of transmitted light, I, is measured and transmitted to the recorder which registers it in the form of a graph (spectrum), with the intensity I plotted as the ordinate and the wavelength or frequency as the abscissa.

The measurement procedure described is characteristic of so-called single-beam instruments. The operation of current spectrophotometers is based on the double-beam principle, which consists in the following. The radiation detector and the recording device register not only the intensity of light, I, transmitted through the substance but also the incident intensity I_0. The signal is recorded either as the difference $I_0 - I$ or as the ratio I_0/I; measures must be taken in order that both light beams—incident and transmitted—be optically equivalent. When the absorption spectra of solutions are measured, one beam (I_0) passes through a cell (cuvette) full of pure solvent (a reference substance), and the other (I) through a cell containing a solution of the substance under study.

When working in the ultraviolet spectral region, use is made of quartz optics, and in the infrared, salt prisms are employed (prisms made of NaCl, LiF and KBr, depending on the wavelength); the common radiation sources are lamps or (in the infrared region) glowing rods made of definite materials.

There are two fundamental laws in spectrophotometry, which describe the absorption of light by matter. These are Lambert's and Beer's laws.

Lambert's law. This law states: The proportion of monochromatic light absorbed by a homogeneous medium is independent of the intensity of the incident light, and each successive unit layer absorbs an equal fraction of the light incident on it. This law is written in the following form:

$$\ln \frac{I_0}{I} = \alpha l \quad \text{or} \quad I = I_0 e^{-\alpha l}$$

or, converting natural to common logarithms,

$$\log \frac{I_0}{I} = kl$$

where l is the path length of the solution (the thickness of solution layer), and k is the extinction coefficient of the absorbing substance (a constant).

Lambert's law ignores the concentrations.

Beer's Law. This law states: The fraction of the incident light absorbed by a solute is proportional to the number of molecules of

the solute in the light path:

$$I = I_0 \cdot 10^{-Ecl} \qquad D = \log \frac{I_0}{I} = Ecl$$

where E is the molar absorptivity (molar extinction coefficient); c is the molar concentration of the substance; D is the optical density.

It should be noted that Beer's law does not hold in all cases. The deviations from Beer's law are accounted for by the different degrees of association, solvation and dissociation of molecules in solutions of different concentration. Therefore, in measuring absorption spectra in solutions of differing concentrations it is necessary to check whether conformity to Beer's law is observed (for example, the double increase of the concentration must be equivalent to the doubled thickness of the absorbing layer at the same concentration).

Light absorption may be registered as graphs in the form of various quantities:

(a) I/I_0 = transmittance (transmission);

(b) $100\ I/I_0$ = percent transmittance;

(c) $I_0 - I/I_0$ and $100\ (I_0 - I/I_0)$ = fraction of absorbed light and percent absorbance;

(d) $D = \log I_0/I$ = optical density (absorbance or extinction);

(e) $E = D/cl$ = molar absorptivity (molar or molecular extinction coefficient), i.e., the optical density of a $1M$ solution for a layer thickness of 1 cm.

In ultraviolet spectra, usually the molar absorptivity E or $\log E$ is plotted on the ordinate, and the wavelength in millimicrons (mμ) or in angstroms (Å) on the abscissa. When infrared spectra are recorded, the percent absorbance or percent transmittance is plotted as the ordinate, and the frequency in reciprocal centimetres (cm^{-1}) or, less often, the wavelengths in microns (μ) as the abscissa

The Physical Meaning of Absorption and Raman Spectra. When light of frequency ν is absorbed by a molecule, the electrons forming the chemical bonds are raised to higher energy levels (the molecule undergoes a transition from the ground state to one of the excited states with a higher energy content, the difference in energy level being given by the relation:

$$h\nu = E_1 - E_0$$

where E_0 and E_1 are the energies of ground and excited states of the molecule.

This extra energy is further dissipated by the molecule as heat or radiation; this however is immaterial in our discussion.

When light energy within the range of the optical spectrum is absorbed, it may increase the vibrational energy of the chemical bonds, the rotational energy of the molecule as a whole (and of parts of it

about the chemical bonds) or the excitation energy of the outer, valence electrons (for the inner electrons to be excited, harder radiation is required). To increase the rotational energy of the molecule, relatively small energy quanta are sufficient, and therefore the corresponding absorption lies in the far infrared region—the region of longer wavelengths (further in the text we shall not discuss the rotational spectra since they are seldom used in organic chemistry). The

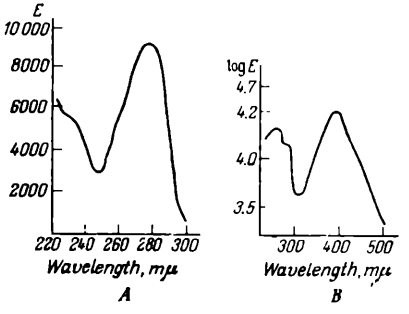


Fig. 6.15.

The ultraviolet (UV) spectra in alcoholic solution:
A— caffeine; *B*—crotonaldehyde.

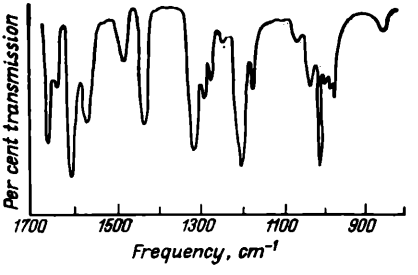


Fig. 6.16.

The infrared (IR) spectrum of benzalacetophenone.

energies which are required to increase the vibrational energy of the molecule (i.e., to increase the amplitude of vibration of the atomic nuclei in the bonds) are provided by radiation in the near infrared region.

Higher energy quanta are required to excite the outer electrons of the molecule (absorption in the visible and ultraviolet regions). The quanta required to change the electronic energy are about one or two orders of magnitude higher than those required to change the vibrational energy. Therefore, absorption in the ultraviolet region causes electronic, vibrational or rotational transitions; absorption in the long-wavelength infrared region is accompanied by the change of the rotational energy alone.

The change of the energy of the molecule caused by absorption of light (energy transitions) is presented in Fig. 6.17, which shows electronic and vibrational levels (for each purely vibrational transition there is a progression of closely spaced rotational levels not shown in the diagram of Fig. 6.17). The maxima in the absorption spectra correspond to the most probable transitions between the energy levels of the molecule. Each maximum refers to a definite type of electronic or vibrational excitation of the molecule.

From the above reasoning and Fig. 6.17 we may conclude that electronic spectra are the most complicated since they show simul-

taneously the vibrational and rotational "fine structures". The vibrational fine structure is in fact observed in the electronic spectra of molecules in the gas phase and only seldom in solutions (Fig. 6.18). The same may be said about the rotational fine structure of the vibrational spectrum.

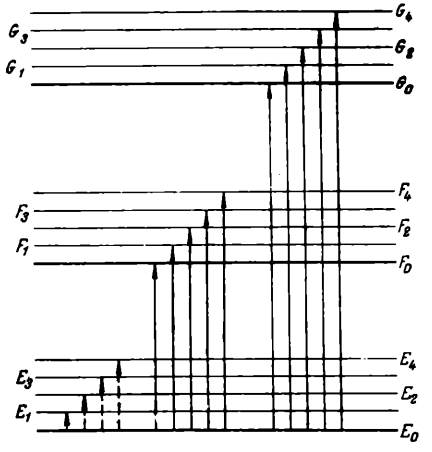


Fig. 6.17.
Excitation of molecules on adsorption of a light quantum:
E_0 — ground electronic state; G, F — excited electronic states; E_1-E_4 — excited vibrational states of the ground electronic state. It is seen that $E_n - E_0 \ll F_n - F_0$. The scheme is arbitrary: the distances $E_n - E_{n-1}$, $F_n - F_{n-1}$, etc., are far from being equal.

Thus, absorption spectra are intimately associated with the structure of the molecule: vibrational spectra with vibrations of atoms in the molecule about the equilibrium positions, and ultraviolet spectra and spectra in the visible region with excitation of valence electrons in the molecule. Each absorption maximum corresponds to a definite type of electronic or vibrational excitation of the molecule. Certain maxima are so characteristic of some groups of atoms or bonds that the position of these maxima varies little from molecule to molecule. Such are, for example, the valence vibrations of the bonds: C=O (about 1700 cm^{-1} in the infrared region), C=N (ca. 2250 cm^{-1}), O—H (3550-3650 cm^{-1}). They are called characteristic

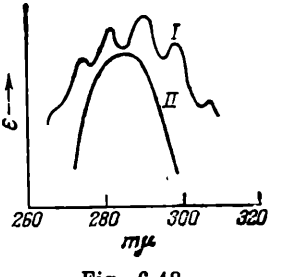


Fig. 6.18.
The ultraviolet spectrum of acetaldehyde in the gas phase (*I*) and in alcoholic solution (*II*). The spectrum *I* shows the fine structure.

maxima and enable determining the presence or absence in the molecule of the various groups of atoms or bonds.

Combination-scattering or Raman spectra are also vibrational spectra. They are studied by measuring the spectrum of the radiation

scattered by the substance under examination. In practice, the following procedure is used. A sample of a pure liquid or solution is irradiated with light of certain wavelength (the magnitude of wavelength is not so important) and the spectral composition of the radiation scattered usually at an angle of 90° is investigated. A very intense line of the source of light scattered with a constant wavelength appears in the spectrum. There is a series of weak lines (Stokes lines) on one side of the parent line, and even less intense anti-Stokes lines on the other side, which are arranged symmetrically with respect to Stokes lines at the same distance from the intense parent line (Figs. 6.19 and 6.20).

Use is almost invariably made of more intense Stokes lines. The spacing between the maxima of these lines (expressed in frequency units) and the centre of the parent line is exactly the frequency of the Raman spectrum, known as the **Raman frequency** or the **Raman shift.**

When light is dispersed in a molecular medium, two cases are possible. In the first case, light quanta are scattered unchanged (elastic Rayleigh scattering). This gives rise to a line of the same frequency ν_0 (of the same wavelength λ_0) as the incident radiation (Rayleigh line) in the spectrum. In the second case, as a result of the interaction (energy exchange) between the incident light and the molecule, the light scattering has a different frequency ν_k (inelastic scattering). The frequency difference corresponds to the vibrational frequency of the molecule. This difference is positive (Stokes lines) if the scattering of light is accompanied by an increase in the vibrational energy of the molecule. In this case, as a result of inelastic scattering, the molecule is raised to one of the excited vibrational levels (E_1, E_2, etc., Fig. 6.21). The difference $\Delta\nu_k$ is negative if the molecule became excited and was on one of the excited vibrational levels (anti-Stokes lines). In this case, the vibrational energy is picked up by the incident light and its energy and, hence the scattered frequency, increases ($\Delta\nu_k < 0$). Since the fraction of excited molecules is small as compared with that of unexcited molecules, the intensity of anti-Stokes lines is lower than that of Stokes lines.

Vibrational Spectra. Thus, two spectroscopic methods are found to be associated with the transition of the molecule to the various vibrational energy levels—infrared and Raman spectroscopy. Either method can supplement or complement the other. In order to obtain the complete vibrational spectrum of the molecule, it is necessary in most cases to study both infrared and Raman spectra.

In molecules with n atoms there are possible altogether $3n$—6 independent vibrational motions (the number 6 excludes concerted motions of atoms which result in the movement of the entire molecule in space, i.e., in three dimensions). Each mode of vibration might be expected to be represented by a definite absorption band

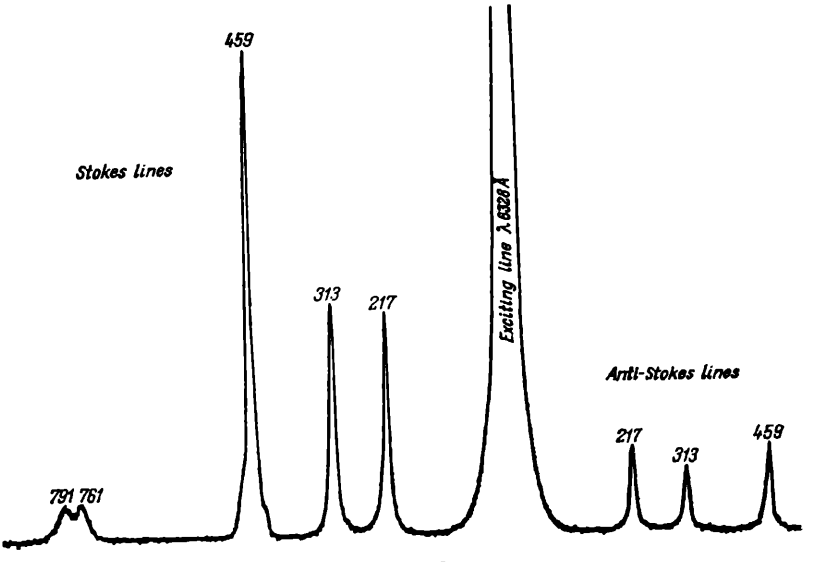


Fig. 6.19.

The combination-scattering spectrum of CCl_4 (laser spectrometer Coderg-PHO).

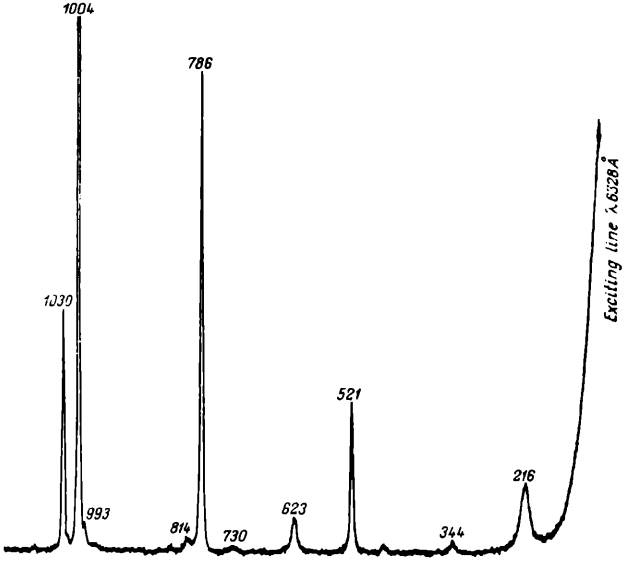


Fig. 6.20.

The combination-scattering spectrum of toluene in the region of up to 1100 cm^{-1} (Coderg-PHO spectrometer).

in the absorption spectrum (the corresponding light quantum induces exactly this vibrational mode). In fact, part of the bands do not appear in the infrared spectrum if the corresponding energy transitions are "forbidden". For absorption in the infrared spectral region it is necessary that the corresponding vibration of the atoms in the

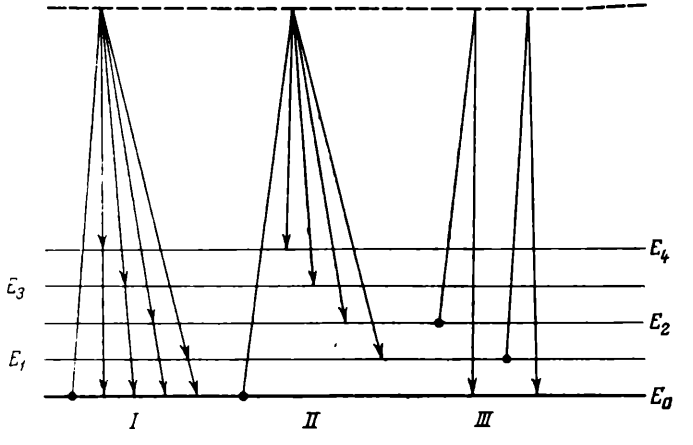


Fig. 6.21.

Combination scattering of light. Energy transitions corresponding to: *I*— excited line of light source (Rayleigh scattering); *II*— Stokes lines; *III*— anti-Stokes lines.

molecule be associated with the change of the dipole moment of the molecule. For this reason, certain modes of symmetrical vibrations are forbidden in the infrared spectrum. Conversely, it is precisely these vibrations that are, as a rule, "active" and most characteristic of the Raman spectrum. For example, in acetylene three modes of valence vibration are possible:

(1) ← H ← C — C → H → Stretching vibration of the C—C bond

(2) ← H — C →← C — H→ Symmetrical stretching vibration of the C—H bond

(3) H →← C ← C — H → Antisymmetrical vibration of the C—H bond

The dipole moment of the molecule varies only in the case of vibrations of the third type. Therefore, only the frequency of these vibrations appear in the infrared spectrum, and the first and second vibrational modes are forbidden. Conversely, in the Raman spectrum the first two modes of vibration are allowed, and vibrations of the third type are forbidden.

The number of lines in the spectrum may also decrease due to the overlap of separate closely spaced bands.

Two principal modes of vibration are possible for molecules: valence and deformation vibrations. The vibrations of atoms along the axis connecting their centres (i.e., of the expansion-contraction type) are called **valence vibrations.** In a diatomic molecule, this is the only mode of vibration possible. Vibrations in which the bond angle varies with time are known as **deformation** or **bond-bending vibrations.** In the benzene molecule, for example, two types of deformation vibrations of the C—H bond are possible: planar and nonplanar vibrations:

Planar Nonplanar

The stretching vibration of a system of two bonded atoms may be likened to the vibration of two balls with masses m_1 and m_2 at the ends of a spring which compresses at a frequency of ν according to Hooke's law for a harmonic oscillator:

$$\tilde{\nu} = \frac{1}{2\pi}\left(\frac{k}{\mu}\right)^{1/2}$$

where k is the force constant of the bond; and μ is the reduced mass of the system given by $\mu = m_1 m_2/(m_1 + m_2)$.

According to the laws of quantum mechanics, the energy of such an oscillator is given by the following expression:

$$E_v = \left(v + \frac{1}{2}\right) h\tilde{\nu}$$

where v is the vibrational quantum number which assumes integer positive values ($v = 0.1$).

For a harmonic oscillator, only those transitions between the states are "allowed", whose quantum numbers differ only by unity, i.e., transitions with $\Delta v = 1$. The transition energy upon absorption is equal to

$$\Delta E_v = \left[(v+1) + \frac{1}{2}\right] h\tilde{\nu} - \left[v + \frac{1}{2}\right] h\tilde{\nu} = h\tilde{\nu}$$

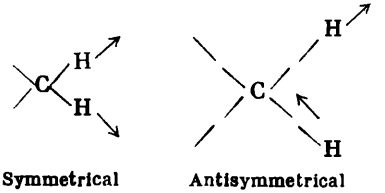
Such transitions give rise to so-called **fundamental bands** which determine the general pattern of the absorption spectrum. Real oscillators in the molecule have an anharmonic character, and therefore the absorption spectrum shows not only transitions with $\Delta v = \pm 1$, but also those with $\Delta v = \pm 2$; ± 3, etc., and transitions accompanied by the excitation of two or more vibrations simultaneously. The bands of such vibrational transitions (overtones and combination bands) are, as a rule, considerably weaker.

Hooke's formula can be used to approximately calculate the frequency of the characteristic absorption band. To do this, one must know the force constant k and the masses of the atoms. In polyatomic molecules, however, such a simplified calculation will be rather approximate since the other atoms surrounding the bond under examination are not taken into account.

Valence Vibrations of Individual Bonds. The absorption bands corresponding to the vibrations of single C—C bonds are, as a rule, non-characteristic, i.e., vary significantly in going from one molecule to another. The valence and valence-deformation vibrations of the carbon skeleton lie predominantly in the region of 600-1300 cm^{-1}. The lines of this region are different and specific even for related molecules. It is for this reason that it is sometimes called the **fingerprint region** of the molecule. Though the fingerprint region cannot be always used for elucidation of molecular structure, it is most convenient and very useful for identifying individual substances. The valence vibrations of the single bonds C—O, C—N, N—O are also found to be in this region.

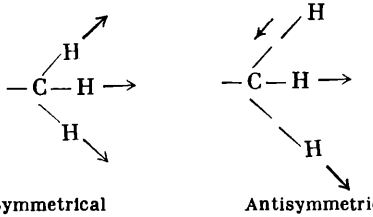
Conversely, the absorption frequencies of the double bonds C=C, C=O, N=O are characteristic, i.e., differ little for different molecules and lie in the region of 1500-1950 cm^{-1}. The absorption of triple bonds is in the even shorter-wavelength region: for example, at 2100-2250 cm^{-1} for the C≡C bond. The vibration frequencies of the bonds C—H, O—H and N—H are also characteristic and the corresponding absorption bands are intensive. The stretching frequency for the hydroxyl group, which is not involved in hydrogen bonding, lies between 3590 and 3650 cm^{-1}; in secondary amines the band of the N—H stretching vibration lies in the range of 3300-3500 cm^{-1}; C—H bonds absorb near 3000 cm^{-1}, the absorption being different for the methyl, methylene and methine groups; besides, it depends on whether a single, double, or triple bond links the carbon atom to the adjacent atom.

In the methylene group, two types of valence vibrations of the C—H bond are possible: symmetrical and antisymmetrical stretching vibrations. In symmetrical valence vibrations both hydrogen atoms simultaneously approach and move away from the carbon atom; in the antisymmetrical stretching vibration, one hydrogen atom moves towards the carbon atom while the other is receding from it:



Symmetrical Antisymmetrical

The same vibrational modes are observed for the methyl group:

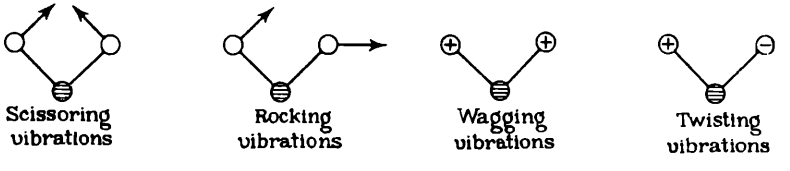


and also for the primary amine group. In paraffins, the symmetrical and antisymmetrical vibration bands are clearly distinguished:

	Symmetrical	Antisymmetrical
Frequency of CH_3	2872 cm^{-1}	2962 cm^{-1}
Frequency of CH_2	2853 cm^{-1}	2926 cm^{-1}

The frequency of the C—H bonds in ethylene hydrocarbons (hydrogen at a double bond) lies higher—in the 3000-3100 cm^{-1} range.

Deformation Vibrations. As has been mentioned, deformation vibrations are accompanied by the change of the bond angles. In benzene, for example, the hydrogen atoms can undergo bond-bending vibrations in the plane of the ring (planar) or out of the ring plane (out-of-plane deformation). The hydrogen atoms of the methylene group may be involved in four types of deformation vibrations:

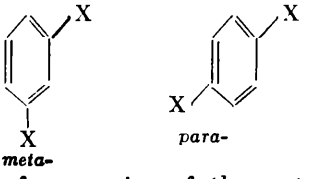


The arrows indicate the direction of movement of atoms in one of the vibration phases: the sign (+) denotes the upward movement above the plane of the drawing; the sign (—) implies the reverse direction; the carbon atom is assumed to be fixed.

Two modes of deformation vibration are possible for the methyl group.

The bands of the deformation vibrations of molecular skeletons lie in the long-wavelength part of the spectrum and are, with rare exceptions, non-characteristic. The bands of the deformation vibrations of bonds of the A—H type (where A=C; N; O) have higher frequencies (from 1650 to 600 cm^{-1}); they are sufficiently characteristic and are used to draw conclusions as to the molecular structure. For example, based on the position of the bands of non-planar vibrations of aromatic C—H bonds in the 680-860 cm^{-1} region one can deduce the position of the substituents in the aromatic ring, for

example:



On the basis of the frequencies of the out-of-plane deformation vibrations of the C—H bonds in olefins one can draw inferences as to the *cis*- or *trans*-structure of these compounds. Acetylene compounds show a characteristic band in the 650-600 cm^{-1} range, which refers to the deformation vibrations of the C—H bond.

Uses of Infrared and Raman Spectra. These spectra are used to identify compounds and to establish the degree of their purity (qualitatively). The infrared spectrum (especially in the fingerprints region) is specific for each molecule, and therefore, as a rule, there is no need in determining the molar absorptivity E (in distinction to ultraviolet spectra). Infrared spectra may also be used for qualitative analysis of mixtures in following the course of reactions and for kinetic measurements.

But the most widespread and important application of infrared Raman spectra in organic chemistry is the elucidation and confirmation of the expected structures of compounds. The presence of almost any functional group in a molecule can be established with the aid of infrared spectra alone. Since the position of the characteristic vibration band is measured within narrow ranges, depending on the nearest environment of the group under examination, one can often not only establish the presence of a functional group in a compound but also to draw inferences as to its neighbours.

Let us consider some examples.

Example 1. *The band of the stretching vibration of the C=O bond.* Table 6.5 gives the frequencies of this line of the spectrum for the various classes of compounds containing a carbonyl group.

It should be noted first of all that the carbonyl band in the infrared spectrum is highly intense and is easily identified. From Table 6.5 it is seen that the frequency increases in going from ketones to aldehydes and esters.

Infrared spectra can provide more detailed information about the environment of the carbonyl group. For example, it is easy to deduce the disposition of electron-attracting groups relative to the carbonyl group. If electron-attracting groups (F, $C \equiv N$, $>C = O$, etc.) are in the α-position, the absorption frequency increases (Table 6.5, Examples 5 and 6); the same is observed for aldehydes. Conversely, if the carbonyl group is conjugated with an aromatic ring or a double C=C bond, then the absorption frequency shifts in the reverse direction by 20-40 cm^{-1}.

TABLE 6.5. The Characteristic Frequencies of the Infrared Spectra of the Carbonyl Group in Various Types of Compounds

Example No.	Type of compound	Frequency range, cm^{-1}
1	Saturated ketones	1725-1705
2	Aryl ketones	1700-1680
3	Diaryl ketones	1670-1660
4	α, β-Unsaturated ketones	1685-1665
5	α-Halogenated aliphatic ketones	1745-1725
6	α-Diketones	1730-1710
7	β-Diketones	1640-1540
8	Aliphatic aldehydes	1740-1720
9	α-Unsaturated aldehydes	1705-1680
10	Aromatic aldehydes	1715-1695
11	Esters of fatty acids	1750-1730
12	Esters with electron-attracting groups in the α-position	1770-1745
13	Metal carbonyls	
	bridging CO group	<1900*
	one-bond	1900-2150

* See Volume IV, "Organoelement Compounds".

Figure 6.22 shows the spectrum of an ester with a strong electron-attracting substituent ($\nu_{C=O}$ 1787 cm^{-1} instead of the usual absorption frequency 1740 cm^{-1} for esters), and Fig. 6.23 gives the spectrum of an unsaturated aldehyde (shifting of the carbonyl absorption band to the low-frequency region). The spectrum of the unsaturated aldehyde also shows a lower peak at 1650 cm^{-1} corresponding to the stretching vibrations of the C=C bond.

The stretching vibration band of the C=O bond is convenient for quantitative determinations, for example, for kinetic measurements or for control of the course of reactions.

Example 2. *Stretching vibrations of the O—H bond.* The absorption band of the hydroxyl group is highly characteristic and lies, as a rule, in the region 3650-3500 cm^{-1} where there are a few other absorption bands. The hydroxyl group usually forms intra- and intermolecular hydrogen bonds. As the strength of these bonds increases the intensity of the absorption band increases and the band shifts to the low-frequency region and broadens. The narrow band at 3650-3550 cm^{-1} is characteristic of a hydroxyl group with a non-hydrogen bonding. The number of intermolecular hydrogen bonds changes

with the concentration of the solution and depends on the nature of the solvent, and therefore the shape and position of this absorption band depends on these factors as well. Strong intramolecular

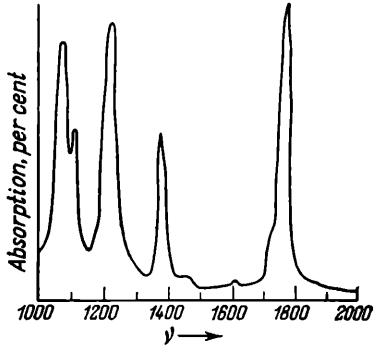


Fig. 6.22.

The infrared spectrum of the ester $CHF_2CFClCOOCH_3$ in a thin layer: $\nu_{C=O}$ = 1785 cm^{-1}.

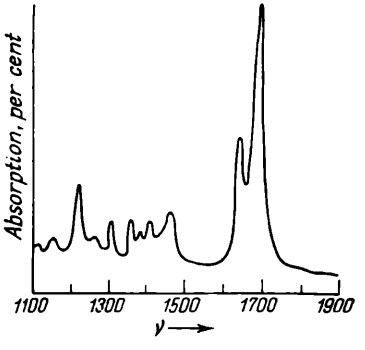


Fig. 6.23.

The infrared spectrum of the aldehyde $CH_3CH_2CH=C(CH_3)CHO$ in a thin layer: $\nu_{C=C}$ = 1650 cm^{-1}; $\nu_{C=O} \cong$ $\cong$1710 cm^{-1}.

hydrogen bonds displace the absorption band to the 2500-3200 cm^{-1} region (for example, in chelates).

Example 3. *Aromatic compounds.* One has often to determine the nature of substitution in the aromatic ring, for example, to establish whether the substitution has taken place in the ortho-, meta-, or para-position relative to the first substituent. To solve this problem, use is often made of absorption bands in the 700-860 cm^{-1} range corresponding to the out-of-plane deformation vibrations of the C—H bonds. In the case of ortho-disubstituted compounds the intense band lies in the 770-735 cm^{-1} range. For meta- and para-disubstituted compounds it is shifted to the higher-frequency region: 810-750 cm^{-1} and 860-800 cm^{-1}. Determination of the structure from this band becomes difficult if it is found to be at the borderline between the ranges (ca. 800 cm^{-1} or ca. 740 cm^{-1}); however, other bands in this or other regions of the spectrum may then be helpful.

If the spectra of reference compounds are known, one can then determine the relative content of isomers (ortho-, para-, meta-) in the mixture. This may be very important, for example, in the determination of the orienting effect of substituents in reactions or for the elucidation of the relative amounts of isomers formed under different conditions.

Raman spectra are used for analogous purposes.

Electronic Spectra. Electronic absorption spectra covering the range from 100 to 800 nm should be subdivided into three regions:

the visible (400-800 nm), the near ultraviolet (200-400 nm) and the far, or vacuum, ultraviolet (200 nm and lower). In organic chemistry, use is commonly made of the spectral range from 220 to 800 nm. The vacuum ultraviolet region, a very important spectral region, is accessible only with special vacuum spectrophotometers.

The excitation of a molecule caused by the absorption of a quantum of energy brings about a rebuilding, generally speaking, of the entire electronic cloud, but in fact only the orbital of valence electrons is changed.

The excitation process may be described approximately with the aid of a model of one-electron transitions. Valence electrons occupy molecular orbitals, the energies of which can be calculated by approximate methods of quantum chemistry. In the ground state of the molecule, the electrons are arranged (in pairs, as a rule) in the lowest-energy molecular orbitals. During the excitation process, the electrons are raised to higher-energy unoccupied orbitals. Three types of electronic transition are distinguished.

(a) $N \rightarrow V$ **Transitions.** This type of transition is associated with the promotion of an electron from a bonding orbital to an antibonding orbital. The excited state is polarized. This means that the electronic transition is accompanied by a considerable change of the dipole moment and the corresponding band is very intense. The $N \rightarrow V$ transitions for bonding σ-electrons ($\sigma \rightarrow \sigma^*$ *transitions*) lie in the vacuum ultraviolet region. The corresponding $\pi \rightarrow \pi^*$ *transitions* require a lower excitation energy and lie in the near ultraviolet, visible, and sometimes even in the near infrared region of the spectrum.

The absorption bands corresponding to $\pi \rightarrow \pi^*$ transitions are characterized by high intensity; the coefficients ε usually exceed 1000. In polar solvents, the absorption is shifted in this case to longer wavelengths.

(b) $N \rightarrow Q$ **Transitions.** This type of electronic transition involves the excitation of an electron from a nonbonding orbital to an antibonding one. The most common type of $N \rightarrow Q$ transitions is the transition of an electron of an unshared pair to the excited π-orbital ($p \rightarrow \pi^*$ *transition*). These transitions lie in a longer-wavelength region than $\pi \rightarrow \pi^*$ transitions and are of lower energy. The corresponding extinction coefficients ε are usually lower than 100. In polar solvents, the absorption shifts to shorter wavelengths. The same effect is caused by the introduction into the molecule of electron-releasing substituents. It is on the basis of this and a number of other features that we can distinguish $p \rightarrow \pi^*$ transitions from $\pi \rightarrow \pi^*$ transitions.

(c) **Atomic or Rydberg Transitions.** If the excitation energy is high, an electron can be ejected from the valence shell of the molecule. At very high excitation energies the molecule loses an ele-

ctron, i.e., photoionization occurs. Rydberg transitions show up in the vacuum ultraviolet region and are represented by high-intensity, rather narrow bands.

Of the greatest interest to organic chemistry are the first two types of electronic transition, (*a*) and (*b*).

Often, the perturbation of an electron orbital caused by the absorption of a quantum of energy is limited to a small part of the molecule. This is a basis of the crude interpretation of the observed absorption bands as transitions of the electrons of individual bonds or groups of bonds in the molecule. This approximation is very fruitful in a number of cases. For example, the absorption in the region of 1700-2100 Å in the spectra of mono-olefins refers to the excitation of the π-electrons of double bonds ($\pi \rightarrow \pi^*$ transitions). The number of isolated double bonds in the molecule does not practically affect the position of this band, and only its intensity increases proportionately. If the number of conjugated double bonds increases, the band of a $\pi \rightarrow \pi^*$ transition is displaced to the longer-wavelength region of the spectrum. Such a movement is often described as a **bathochromic shift.** A sufficient lengthening of a conjugated system of bonds can alone displace absorption maxima to the visible spectral region and the compound becomes coloured (Tables 6.6 and 6.7).

TABLE 6.6. **Values of λ_{max} for Molecules with Different Conjugation Chain Lengths**

Compound	λ_{max}, nm				
	$n = 1$	$n = 2$	$n = 3$	$n = 4$	$n = 5$
$CH_3-(CH=CH)_n-COOH$ (in alcohol)	204	254	294	327	—
$CH_3-(CH=CH)_n-CHO$ (in alcohol)	220	271	315	353	393
$C_6H_5-(CH=CH)_n-C_6H_5$ (in benzene)	306	334	358	384	420
Values of $\varepsilon \cdot 10^{-3}$ for the last example	24	40	75	86	114

Unsaturated groupings responsible for the absorption in the spectral region indicated, for example, C=C, C=O, C=N, N=N, C=S, are called **chromophores** (or *chromophoric groups*).

The attachment of electron-releasing groups, especially those possessing unpaired electrons, causes a bathochromic shift of absorption bands (corresponding to $\pi \rightarrow \pi^*$ transitions). Groups which do not in themselves show high-intensity absorption bands (200-800 nm) and yet cause a bathochromic shift of the bands responsible for the $\pi \rightarrow \pi^*$ transition of chromophores are called **auxochromic groups** or **auxochromes.** The most typical auxochromes are $\ddot{N}H_2$, $\ddot{N}R_2$, $\ddot{O}H$, $\ddot{O}R$, $\ddot{S}H$, $\ddot{S}R$.

TABLE 6.7. Values of λ_{max} and ε for a Series of Hydrocarbons with Amount of Conjugation Increasing from Compound to Compound

Compound	Number of conjugated bonds	λ_{max}, nm	$\varepsilon \cdot 10^{-3}$	Colour
Butadiene	2	217	21	Colourless
Hexatriene	3	258	35	Ditto
Decatetraene	4	310	42	Ditto
Vitamin A	5	328		Ditto
Tetradecahexaene	6	360	70	Ditto
α-Carotene	10	445	145	Orange

The absorption band responsible for the $\pi \rightarrow \pi^*$ transition is called a *K*-band. In the case of conjugated systems there is one common *K*-band instead of several bands. From the position and intensity of this band one can, generally speaking, deduce the length of the conjugated system (see Tables 6.6 and 6.7).

The absorption intensity is associated with the change of the dipole moment during the excitation; it is natural that in the case of long conjugated systems the dipole moments of excited dipolar states must be greater. On the other hand, for the π-electrons of long conjugated systems to be excited, a lower energy is required; this is what accounts for the bathochromic shift.

In the case of carbonyl compounds (aldehydes, ketones, esters, etc.), apart from the intense *K*-band, there is a low-intensity band of the $p \rightarrow \pi^*$ transition, which lies in a longer-wavelength spectral region. It differs from the *K*-band not only by the lower intensity; its "behaviour" is also different from that of the *K*-band. For example, with increasing polarity of the solvent the band of the $p \rightarrow \pi^*$ transition undergoes a **hypsochromic shift** (is moved to shorter wavelengths), while the *K*-band ($\pi \rightarrow \pi^*$ transition) usually shifts to longer wavelengths.

Benzene shows three absorption bands: $\lambda_{max} = 180$ nm ($\varepsilon = 47{,}000$), 200 nm ($\varepsilon = 7400$) and 260 nm ($\varepsilon = 220$). Using conventional instruments, one can examine only the last two bands: *K* and *B*. The *K*-band is assigned to dipolar excitation (the *K*-band of polyenes), and the low-intensity *B*-band is regarded as representing the "forbidden" biradical excitation. Any substituent causes a bathochromic shift of the *K*- and *B*-bands and enhances their intensity, though these effects significantly differ qualitatively from substituent to substituent.

The spectrum of benzene is especially strongly affected by substituents capable of conjugation. These are groupings containing double bonds, atoms bearing unpaired electrons (NH_2, OH, etc.) and, finally, electron-attracting groups such as NO_2, C=O, etc.

According to the magnitude of the bathochromic effect, ortho-para and meta substituents may be arranged in the following two series:

$$-CN < -SO_2R < -COOH < -COCH_3 < -CHO < -NO_2$$
$$Cl < OH < SR < NR_2$$

Evidently, the bathochromic shift increases with increasing tendency of groups towards conjugation. When different types of substituents (capable of conjugation) are in the *para*-position, the bathochromic shift is especially strong: $\lambda_{max} = 230$ nm for aniline (aminobenzene); 269 nm for nitrobenzene; 266 nm for *p*-dinitrobenzene; *p*-nitroaniline has an intense absorption maximum at 381 nm (!), whereas the λ_{max} of *m*-nitroaniline is 280 nm. Such a considerable bathochromic shift of the *K*-band of benzene under the influence of conjugation is used by chemists for the various purposes, for example, for determination of the position of a substituent in the benzene ring, which is required for analysis of mixtures of *meta*- and *para*-substituted compounds.

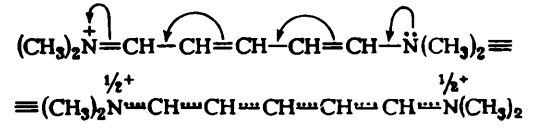
As we shall see further, such a conjugation of electron-attracting and -releasing groups is observed in numerous dyes; not only aromatic rings but also ordinary systems of conjugated bonds can be involved in the conjugation chain.

Ultraviolet spectra are well known for all ordinary classes of compounds. For example, we know the spectra of various heterocyclic compounds and their derivatives, fused-ring (condensed-ring) systems, many steroids, terpenes. Specific empirical rules have been worked out, which enable us to deduce the position of substituents or double bonds.

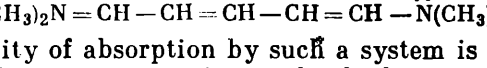
Colour of Compounds and Dyes. Compounds which absorb light in the visible spectral region (i.e., from 700 to 400 nm) are coloured. The visible colour of a compound is complementary to that absorbed. For example, if the absorption maximum lies in the region of 400-435 nm (violet rays are absorbed), the colour of the compound is yellow-green. The absorption of the yellow colour at 580-595 nm gives rise to the dark-blue colour. The bathochromic shift, i.e., the movement of an absorption band to longer wavelengths is called the deepening of colour, while the hypsochromic shift is known as the increase of colour or tint. So, the change from yellow to red, violet, dark blue and, finally, to green is the colour deepening.

As has been indicated, the lengthening of the chain may lead to absorption in the visible region of the spectrum and to the appearance of a colour. This is observed, for example, in carotenes (see Volume IV). There are eleven conjugated bonds in β-carotene (λ_{max} 483 and 453 nm). Though the colour intensity of compounds of this type is high, it is insufficient for their practical utilization as dyes (let alone the fact that dyes must be capable of firmly binding with the fibre).

Of special importance for dyes is the presence at the ends of the conjugated chain of two groups capable of conjugation but of opposing nature (in the sense of electronegativity). This is responsible for the conjugation of these two groups through the entire conjugated chain and for the delocalization of charge over these groups. *p*-Nitroaniline mentioned above may be quoted as an example. As a further, more typical example, we may quote azomethine dyes. They are salts with a cation built of a polymethine chain with an odd number of —CH= units, which has at one end a trivalent nitrogen and on the other, a tetravalent, positively charged nitrogen (or similar groups). The conjugation of the unshared pair of electrons of a trivalent nitrogen with a positive charge through the entire polymethylene chain brings about a uniform delocalization of charge over both nitrogen atoms:



Such a system is naturally characterized by the ease of dipolar excitation of the molecule to one of the polar structures:



The probability of absorption by such a system is very high, and therefore the absorption intensity is also high.

(D) Polarimetry

Of primary importance in studying "optical" stereoisomerism is the measurement of the angle of rotation of the plane-polarized light on passage of a light ray polarized in a certain plane through a layer of a substance or a solution of known concentration. Angles of rotation are measured by instruments called polarimeters. If α = observed angle of rotation (in degrees), l = layer thickness, through which the light is passed (in decimetres), c = solution concentration (g/ml), d = density of the liquid (g/cm^3), λ = light wavelength, $[\alpha]_\lambda^t$ = specific rotation at a given temperature and λ, then

$$[\alpha]_\lambda^{t^\circ} = \frac{100\alpha}{lc} \text{ (for solutions)} \qquad [\alpha]_\lambda^{t^\circ} = \frac{\alpha}{lc} \text{ (for liquids)}$$

The molecular rotation [M] is given by

$$[M]_\lambda^{t^\circ} = \frac{[\alpha]_\lambda^{t^\circ} m}{100}$$

where m is the molecular weight of the substance under study.

As has already been stated, the values of $[\alpha]$ and, hence [M], are equal in absolute value but opposite in sign for optical antipodes under identical conditions. Under different conditions, for example, in different solvents, $[\alpha]_\lambda^t$ and $[M]_\lambda^t$ may vary and even change their sign.

Diastereomers generally possess different $[\alpha]_\lambda^t$ and $[M]_\lambda^t$. Molecules which contain asymmetric carbon atoms but have a plane of symmetry do not rotate the polarization plane, i.e., $[\alpha]_\lambda^t = 0$ and $[M]_\lambda^t = 0$. In a more general form, the molecule is asymmetric if it has neither a plane nor an axis of symmetry. A compound consisting of such molecules rotates the plane of polarized light in the liquid and in the gaseous state. Even from this it is clear what a powerful means of investigating stereoisomerism is the measurement of the angles of rotation of the plane of polarized light (see, for example, under "Stereochemistry of Monosaccharides").

L. A. Chugaev who extensively used a comparison of molecular rotations of a number of compounds established that in a series of homologues and derivatives of optically active compounds the molecular rotation remains constant (with exception of the first members of the series). For example, the values of molecular rotation for esters of optically active amyl alcohol (2-methyl-1-butanol) are as follows:

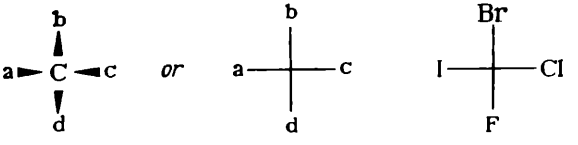
	[M]		[M]
Formate	3.96°	Valerate	4.33°
Acetate	2.33°	Caproate	4.46°
Propionate	3.99°	Laurate	4.21°
Butyrate	4.25°	Stearate	4.49°

Chugaev also worked out a rule (known as the distance rule), according to which optical activity is most strongly affected by substituents directly attached to the optical centre, this effect decreasing rapidly as the substituents move away along the chain.

Based on the intensive preliminary work and a number of attempts (L. A. Chugaev, Eyring, W. Kuhn), Brewster (1959) succeeded in correlating, in an empirical quantitative way, the structure, configuration, and conformation of a molecule with its optical activity, namely, with the value of [M]. The quantity [M] was found to be a function of the polarizability of the groups linked to an asymmetric centre, the polarizability being functionally related (as previously mentioned) to the molecular and atomic refractions.

If the carbon atom is found to be linked to atoms, such as the halogens, the rotation of which about the valence bond as the axis does not change anything, or to groups, like the methyl, hydroxyl and other simple groups, the rotation of which about the bond of their key atom with an asymmetric carbon changes the conformation insignificantly, the sign of rotation can be predicted. For this to be done, it is necessary to arrange (Fischer projection) the projection

of a molecule with an asymmetric carbon atom in such a way that atom [a] is the most polarizable (as known, in the Fischer projection, a single interchange of two substituents gives rise to an antipode, and two such interchanges do not alter the configuration), and the other atoms are arranged, as far as possible, in the clockwise direction in the order of decreasing polarizability:

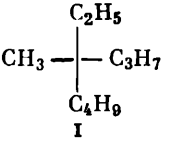


Such an arrangement is given in the formula IBrClF on the right. It corresponds to the *dextro*-rotation denoted by the sign (+). The reverse arrangement corresponds to the *levo*-(—) rotation.

Below are given the atomic refractions for one atom linked to an asymmetric carbon in a number of groups, i.e., the values that should be taken into account in calculating the sign of rotation:

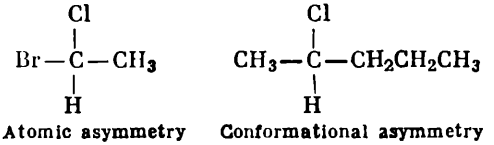
I	13.954	C≡N	3.580	NH_2	2.382
Br	8.741	C=C	3.379	OH	1.518
SH	7.729	C_6H_5	3.379	H	1.028
Cl	5.844	COOH	3.379	D	1.004
C≡C	3.580	CH_3	2.591	F	0.81

This applies to cases where relatively simple groups or atoms are attached to the asymmetric carbon atom. According to this calculation, the rotation, say, of the antipodes of saturated hydrocarbons with an asymmetric carbon atom, like compound I, must have



I

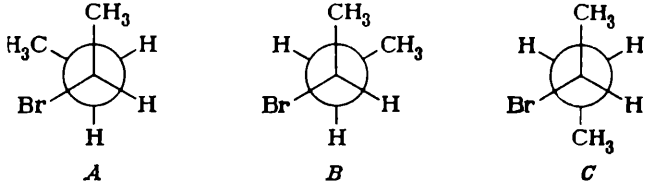
been equal to zero since the polarizability of all saturated carbon atoms attached to the asymmetric centre is identical. This is however not the case in reality: in this particular case, $[M]_D = -9.9°$. Here we have to take into account the "conformational asymmetry", the contribution of which, as will be shown below, can be estimated quantitatively. An example is:



Atomic asymmetry Conformational asymmetry

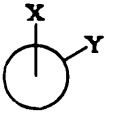
Naturally, cases are possible when both types of asymmetry are present. The total molecular rotation will then be the sum of the contributions of the atomic and conformational asymmetry. The contribution of conformational asymmetry can be calculated, whereas that of atomic asymmetry is subject only to qualitative estimation. It should be noted that the atomic contribution can often be determined experimentally since the angles of rotation of many simple compounds are well known.

The meaning of "conformational asymmetry" consists in the following. Different conformations of the same compound have different symmetry and different statistical contribution (i.e., their percentage content is different). Therefore the total effect on the polarization of light will depend on the arrangement of atoms in different conformations and also on the statistical contribution of the conformation. For example, in the case of $CH_3CH_2\overset{*}{C}H(CH_3)Br$ there is only conformational asymmetry since two identical atoms (C) are situated at the asymmetric centre. For this compound there are three possible staggered conformations:



Conformation *A* is excluded because it is unfavourable (has a small contribution): all the three substituents in it are in the skew position (rule 1) (see below). Let us estimate the contribution of each of the other two conformations.

It is postulated that the fragment makes a contribution of $+kXY$, where k is a constant equal to 160, and $X = \sqrt{R_X}$, $Y = \sqrt{R_Y}$ (here R_X and R_Y are the atomic refractions of atoms X and Y).



Let us perform, according to Brewster, a round about each conformation in the clockwise direction as follows (the transfer from the top atom to the bottom one is denoted by the plus sign, and the

reverse transfer, by the minus sign):

$$\Delta [M]_B = 160(C\cdot C - C\cdot H + H\cdot H - H\cdot Br + H\cdot Br - H\cdot C) =$$

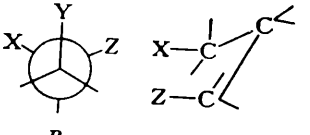
$$= 160\,(C-H)^2 = 160\,(\sqrt{R_C} - \sqrt{R_H})^2$$

$$\Delta [M]_C = 160(C\cdot H - H\cdot H + H\cdot C - C\cdot Br + Br\cdot H - H\cdot C) = -160(Br-H)\,(C-H)$$

$$[M] = k\frac{\Delta [M]_B}{2} - k\frac{\Delta [M]_C}{2} =$$

$$= 160\,\frac{(\sqrt{R_C} - \sqrt{R_H})^2 - (\sqrt{R_{Br}} - \sqrt{R_H})(\sqrt{R_C} - \sqrt{R_H})}{2}$$

In the previous case, there were only three conformations but if the chain of carbon atoms is longer, the number of conformations sharply increases. The calculation according to Brewster for such compounds is more complicated and requires the building of three-dimensional models. This method is discussed in more detail in the original articles by Brewster. Here we can only say that the calculation involves a comparison of the possible conformations and the energetically less favourable conformations of the *D* and *E* types in which the substituents X, Y and Z are more bulky than H.



D *E*

The other conformations are believed to be equally probable since it is not possible to estimate their relative statistical contributions. In spite of such an approximation, the calculated data are in good agreement with experiment.

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Academician ALEKSANDR NIKOLAEVICH NESMEYANOV was one of the most distinguished organic chemists of our time. He conducted fundamental research in the field of organoelement chemistry and authored important and original works on organic and theoretical chemistry. The concept of organoelement (elemento-organic) chemistry was introduced by A.N. Nesmeyanov. He devised diazo method of synthesis of organometallic compounds, discovered new classes of compounds, demonstrated relationship between structure and reactivity of metallic derivatives of tautomeric systems. His principal areas of interest were the chemistry of organometallic compounds and general problems of organic chemistry. Nesmeyanov initiated and directed a number of new trends of investigation, one of which was the preparation of synthetic and artificial food. Among the practical achievements in the investigations carried out by Nesmeyanov and his school may be mentioned the development of valuable medicinal preparations, the synthesis of a new antiknock compound and the preparation of a number of materials for special technical applications.

Nesmeyanov was awarded the State Prize for his investigations in the field of organoelement compounds and the Lenin Prize for his remarkable contributions to the development of the science and practical implementation of the scientific achievements in the national economy.

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